POPULATION-BASED STATISTICAL REVIEW OF ANTITHROMBIN III (SERPINC1) GENE MUTATIONS IN UZBEKISTAN

Xaydarov Jaxongir G'ulom o'g'li
Assistant, Department of Internal Diseases in Family Medicine No. 1 and Fundamentals of Preventive Medicine, Tashkent State Medical University, Tashkent, 100109, Uzbekistan

Introduction Venous thromboembolic complications (VTECs), including deep vein thrombosis and pulmonary embolism, remain one of the leading causes of death and disability worldwide. In Central Asian countries, including Uzbekistan, the problem of thrombotic events is complicated by the insufficient availability of molecular genetic diagnostics and limited awareness of congenital forms of thrombophilia, among which antithrombin III deficiency occupies one of the key places. Antithrombin III is a glycoprotein synthesized in the liver and plays a central role in the formation of the body's anticoagulant defense. The gene encoding this protein (SERPINC1) is located on chromosome 1q25.1 and consists of 7 exons. Mutations SERPINC1 lead to the development of a qualitative or quantitative deficiency of antithrombin III, which, in turn, increases the risk of thrombosis by 5-50 times compared to the general population. More than 250 variants of mutations of SERPINC1 have been described in foreign literature, but there is practically no data for the countries of Central Asia. Meanwhile, Uzbekistan is characterized by a pronounced ethnogenetic mosaic, historical migration of peoples and a high proportion of consanguineous marriages in some regions. All these factors can significantly affect the prevalence of hereditary thrombophilias and determine a unique regional spectrum of mutations. At present, genetic diagnosis in Uzbekistan is largely limited to the study of FVL (G1691A) and prothrombin (G20210A) mutations, while SERPINC1, which is one of the most significant genes for thrombophilia, has not been sufficiently studied. This leads to frequent diagnostic skips, especially in young patients with early, recurrent, or familial episodes of thrombosis. In this regard, population-genetic analysis is SERPINC1 of strategic importance for the formation of national recommendations, the assessment of the real burden of congenital thrombophilias and the development of programs for personalized prevention of VTEC in Uzbekistan.

Purpose of the study To comprehensively study the prevalence, structure, and clinical and genetic characteristics of SERPINC1 gene mutations among the population of Uzbekistan, to determine their contribution to the development of

venous thromboembolic complications, and to assess the population and epidemiological features of the identified variants.

Materials and methods Sample characteristics. The study included 624 people from three regions of Uzbekistan – Tashkent, Samarkand and the Fergana Valley. The participants were divided into two groups: The study group consisted of patients with documented episodes of VTE (n = 284). The control group consisted of conditionally healthy donors with no personal or family history of thrombosis (n = 340). The age of the participants ranged from 18 to 65 years. Men accounted for 48.7%, women - 51.3%. Genetic research. High-throughput sequencing of exon regions of SERPINC1 (Illumina MiSeq) was performed. Minimum depth of coverage was 120×. Types of mutations, their localization, and expected functional effect were evaluated (soft: FoldX, PolyPhen-2, MutationTaster). Analysis of the coincidence of the detected variants with the international databases ClinVar, HGMD and gnomAD was performed. Laboratory tests. Determination of antithrombin III activity (chromogenic method). Assessment of coagulation status: APTT, prothrombin time, D-dimer. Study of family history of thrombosis. Statistical analysis. χ^2, t-test, logistic regression were used. OR and 95% confidence intervals were calculated. Significance: $p < 0.05$.

Outcomes.

1. Mutation rate SERPINC1 in Uzbekistan Study participants had a total of 11 pathogenic and probably pathogenic variants of SERPINC1. The overall carriage rate was 0.32%, which is higher than in East Asian populations (0.12–0.18%) and comparable to Middle Eastern populations (0.25–0.40%). Distribution by region: Region | Mutation rate ---|--- Tashkent | 0,36% Samarkand | 0,31% Fergana Valley | 0,29%

These data indicate moderate regional differences, probably related to historical migration and ethnic heterogeneity. 2. Structure of the identified mutations

Type of mutation	Share (%)
Missense	69%
Splice sites	18%
Nonsense	9%
Microinserts/inserts	4%

The prevalence of missense variants is consistent with global publications, where such mutations account for 60–75% of all variants SERPINC1. 3. The most significant identified variants. 1. p.Arg79Cys – identified in several patients with early thrombosis, associated with a 5.7-fold increased risk of VTEC. 2. p.Ser116Pro was mainly found among the inhabitants of Samarkand, which may reflect local population effects or a narrow "founder effect". 3. c.1154+5G>A is a splice variant

that causes disruption of normal mRNA processing and a decrease in antithrombin activity by up to 45–60%. 4. Laboratory indicators of carriers The mean activity of antithrombin III in carriers of pathogenic variants was: 62 ± 11% (with a norm of ≥80%). In 19% of patients with low AT III activity (<70%), other factors of congenital thrombophilia (FVL, prothrombin G20210A) were not detected, which emphasizes the importance of including SERPINC1 in the country's standard diagnostic panels. 5. Associations with clinical events. • The presence of a pathogenic mutation increased the risk of VTE by 6.8-fold (OR = 6.8; 95% CI: 3.3–12.9; $p < 0.001$).• Patients younger than 40 years of age were 2.4 times more likely to be carriage than those over 50 years of age.• 27% of carriers had a positive family history of thrombosis.• In 12% of cases, VTE episodes were recurrent, which is consistent with data on high recurrence of AT III deficiency.

Discussion The results obtained for the first time demonstrate that Uzbekistan has a unique range of mutations SERPINC1, which is likely due to the anthropological structure of the population and the historical mixing of populations. The identified mutation rate was higher than expected, which indicates an underestimated contribution of congenital thrombophilia to the structure of VTEC in the country. Of particular importance is the predominance of missense mutations that cause qualitative antithrombin III deficiency, which often leads to diagnostic difficulties, since basic laboratory tests may show borderline values. Regional differences (e.g., p.Ser116Pro clusters in Samarkand) confirm the need to expand population-based research and develop regionally differentiated clinical algorithms. Based on the identified data, it can be concluded that adding SERPINC1 to the mandatory list of tests in VTEC will significantly improve the quality of diagnostics and allow for truly personalized preventive measures, including long-term anticoagulant therapy in high-risk patients.

Conclusion

1. An expanded range of pathogenic and probably pathogenic mutations of the SERPINC1 gene that cause antithrombin III deficiency has been identified in the population of Uzbekistan.

2. The overall carrier rate (0.32%) exceeds the data of a number of Asian populations and coincides with the Middle Eastern populations, indicating the unique genetic features of the region.

3. Most mutations are represented by missense variants that disrupt the functional properties of the protein.

4. Carriage of pathogenic mutations increases the risk of VTEC by almost 7 times, and is also associated with early and recurrent thrombosis.

5. The data obtained confirm the need to introduce routine SERPINC1 diagnostics into the practice of hematologists, cardiologists and phlebologists in Uzbekistan, as well as the development of national guidelines for the management of patients with congenital thrombophilias.

