New Pharmacogenetic Markers to Predict the Risk of Bleeding During Taking of Direct Oral Anticoagulants

Karin B. Mirzaev¹*, Dmitriy V. Ivashchenko¹, Ilya V. Volodin¹,², Elena A. Grishina¹, Kristina A. Akmalova¹, Anastasia A. Kachanova¹, Alena I. Skripka³, Radik M. Minnigulov³, Tatiana E. Morozova³, Olga A. Baturina³, Alexander N. Levanov⁴, Tatiana V. Shelekhova⁴, Alexey I. Kalinkin², Dmitriy A. Napalkov³, Anastasia A. Sokolova³, Denis A. Andreev³, Igor N. Sychev¹, Pavel O. Bochkov¹, Dmitriy A. Sychev¹

¹Russian Medical Academy of Continuous Professional Education. Barrikadnaya ul. 2/1-1, Moscow, 125993 Russia
²Research Centre for Medical Genetics. Moskvorechiye ul. 1, Moscow, 115522 Russia
³I.M. Sechenov First Moscow State Medical University (Sechenov University). Trubezkaya ul. 8-2, Moscow, 119991 Russia
⁴Saratov State Medical University named after V.I. Razumovsky. Bolshaya Kazachya ul. 112, Saratov, 410012 Russia

Aim. To search for new pharmacogenetic biomarkers of bleeding risk in patients taking rivaroxaban and dabigatran for different indications: atrial fibrillation, endoprosthesis of large joints of lower limbs.

Material and methods. The study enrolled 29 patients (17 patients received dabigatran and 12 – rivaroxaban), who had hemorrhagic complications during taking direct oral anticoagulants. To find new pharmacogenetic biomarkers of bleeding risk, a next generation sequencing (NGS) was performed for selected candidate genes.

Results. Among the patients with bleeding who received dabigatran, 13 variants of the nucleotide sequence showed statistically significant deviation from the population values: 11 in the CES1 gene and 2 in the ABCB1 gene. Among the patients with bleeding who received rivaroxaban, 7 variants of nucleotide sequence showed significant deviation: 4 in the ABCG2 gene, 2 in the CYP3A4 gene, and 1 in the ABCB1 gene.

Conclusion. The identified in this study polymorphisms of candidate genes ABCB1, ABCG2, CES1, CYP3A4 were associated with the risk of bleeding in patients taking rivaroxaban and dabigatran. It makes an important contribution to the pharmacogenetics of direct oral anticoagulants and require additional assessment of clinical significance in further studies.

Keywords: dabigatran, rivaroxaban, pharmacogenetics, direct oral anticoagulants, sequencing, personalized medicine.

The full English version of the article is available on the journal website: www.rpcardio.com

For citation: Mirzaev K.B., Ivashchenko D.V., Volodin I.V., Grishina E.A., Akmalova K.A., Kachanova A.A., Skripka A.I., Minnigulov R.M., Morozova T.E., Baturina O.A., Levanov A.N., Shelekhova T.V., Kalinkin A.I., Napalkov D.A., Sokolova A.A., Andreev D.A., Sychev I.N., Bochkov P.O., Sychev D.A. New Pharmacogenetic Markers to Predict the Risk of Bleeding During Taking of Direct Oral Anticoagulants. Rational Pharmacotherapy in Cardiology 2020;16(5):670-677. DOI:10.20996/1819-6446-2020-10-05

Received: 31.07.2020
Accepted: 12.08.2020

*Corresponding Author: karin05doc@yandex.ru
The direct oral anticoagulants (DOACs: dabigatran, rivaroxaban, apixaban, edoxaban) are now widely used for thromboembolism prevention in patients with non-valvular atrial fibrillation (AF), after knee and hip replacement and for prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). In the USA since 2011 to 2014 prescription of rivaroxaban increased from 0.13% to 13.87%, and dabigatran from 1.3% to 7.6% [1]. The proportion of DOACs among oral anticoagulants in 2017-2018 was 56.5% and 31% in the UK and the USA, respectively [2,3]. In 2018 rivaroxaban and apixaban were among the top 10 best-selling medicines in the U.S.: 10th and 2nd place, respectively [4].

The increase in DOACs use which have a number of benefits in comparison with warfarin (faster onset of action, no need for routine control of pharmacodynamic response, predictable pharmacokinetics, fixed dosage regimen etc.) is associated with the most common adverse event – bleeding including some of them requiring emergency medical care [5]. For example, in the UK, each increase in DOACs prescription by 10% in routine general practitioners practice results in 0.9% increase in hemorrhagic events [5]. At the same time, with the begining of DOACs use 4,929 additional cases of emergency hospitalization due to hemorrhagic events during anticoagulant therapy were registered in this country between 2011 and 2016 [5].

Different clinical and demographic factors (age, renal function impairment, race and ethnicity, gender, smoking, drug interactions, diet, etc.) as well as genetic factors (polymorphism of genes encoding cytochrome P-450 isoenzymes and drug transporters, etc.) contribute to the variability of pharmacological response to DOACs. At the same time, despite the rapid growth of DOACs prescription and the increase in hemorrhagic events during therapy, peculiarities of DOACs pharmacogenetics remain insufficiently studied [6]. Today, there is a limited number of pharmacogenetic studies of the relationship of gene polymorphism of the drug transport system and drug metabolism (ADME) with a response to DOACs: single-nucleotide polymorphisms of CES1 and ABCB1 genes affecting pharmacokinetic parameters and clinical outcomes during dabigatran therapy and single-nucleotide polymorphisms of ABCB1 gene affecting pharmacokinetic parameters of rivaroxaban and apixaban have been detected [7]. However, there is a significant lack of data on the search for new genetic biomarkers through genome sequencing (exom, full genome) or individual candidate genes in patients with an unsatisfactory response and hemorrhagic events due to DOACs.

The aim of the present study was to search for new pharmacogenetic biomarkers of bleeding risk in patients with atrial fibrillation or after hip and knee replacement taking rivaroxaban and dabigatran.

**Material and methods**

Written informed consent to participate in the study has been received from all participants. The study was approved by the local Ethical committee of Russian Medical Academy of Continuous Professional Education.

**Patients**

The study included 29 patients (17 patients received dabigatran and 12 patients – rivaroxaban) from real clinical practice with bleedings classified as 2 or 3 type on BARC scale (Bleeding Academic Research Consortium). Selection of participants was carried out in I.M. Sechenov First Moscow State Medical University (Sechenov University) and Saratov State Medical University named after V.I. Razumovsky. Men accounted for 35.2% in dabigatran group and 75% in rivaroxaban group. The median age was 72.5 [45;86] and 71 [40;87] years in dabigatran and rivaroxaban groups, respectively. Demographic, clinical and laboratory features are presented in Table 1.

**Justification for selecting candidate genes for next-generation sequencing (NGS)**

The initial sample of patients was divided into two groups: a) patients who received dabigatran (n=17) b) patients who received rivaroxaban (n=12). In each group the search for potentially significant variants in target genes was done. According to the literature search on the specialized resource PharmGKB [8] and known pharmacokinetic features of the DOACs from Summary of product characteristics [9]
Pharmacogenetic Markers of Bleeding

**Table 1. Characteristics of the study participants**

| Parameter                                      | Dabigatran (n=17) | Rivaroxaban (n=12) |
|------------------------------------------------|-------------------|---------------------|
| Men, n (%)                                     | 6 (35.2)          | 9 (75)              |
| Age, years                                     | 72.5 [45;86]      | 71 [40;87]          |
| DOAC serum concentration, ng/ml                | 144.3 [36;800]    | 60.1 [24;243]       |
| CHA2DS2VASc score, points                      | 4 [3;7]           | 4.5 [3;8]           |
| HAS-BLED score, points                         | 1 [0;2]           | 3 [1;6]             |
| Hemoglobin, g/l                                | 137 [99;167]      | 125.5 [73;161]      |
| Platelets, 10^9/l                              | 184 [116;246]     | No data available   |
| Thrombocytopenia, n (%)                        | 2 (11.7)          | 0                   |
| GFR, ml/min/1.73 m²                            | 53.5 [31;101]     | 50.5 [16;90]        |
| Dose of DOAC, mg/day                           | 110 [110;220]     | 15 [10;15]          |
| Atrial fibrillation, n (%)                     | 12 (70.6)         | 10 (83.3)           |
| Hip or knee replacement, n (%)                 | 5 (29.4)          | 2 (16.7)            |

Data are presented as Me [25%;75%] or n (%)

DOAC – direct oral anticoagulants, GFR – glomerular filtration rate

*ABCB1* and *CES1* for dabigatran, *ABCB1*, *ABCG2* and *CYP3A4* for rivaroxaban were selected to look for novel pharmacogenetic markers. *ABCB1* gene encodes P-glycoprotein or multiple drug resistance protein, a substrate for which are both rivaroxaban and dabigatran [10]. Rivaroxaban's pharmacokinetics may also be affected by another *ABCG2* transporter that encodes the breast cancer resistance protein (BCRP) [10]. Gene *CES1* encodes carboxylesterase-1, which participates in metabolism of dabigatran to form dabigatran etaxilate. Finally, the gene *CYP3A4*, encodes the isoenzyme of cytochrome system P-450 – *CYP3A4*, a substrate for which is rivaroxaban [10].

**DNA extraction.** DNA was extracted from whole peripheral venous blood samples by selective prescription using high concentrations of salts (“salting-out”).

**Sequencing.** Mutations in patients were screened by high-performance semiconductor parallel DNA sequencing using Ion S5 (Thermo Fisher). In the process of sample preparation we used the standard protocol of preparation by AmpliSeq libraries (Thermo Fisher) with the help of Ion AmpliSeq Library Kit 2.0 reagents and user panel of primers, which includes exons and adjacent intron areas of *ABCB1*, *ABCG2*, *CES1*, *CYP3A4* genes, as well as their 5' and 3’ non-coding areas.

Analysis of sequencing results was carried out using the following software:

1) Torrent Suite consisted of (1.1. Base Caller for primary basic analysis of sequencing results; 1.2. TMAP (Torrent Mapping Alignment Program) for alignment of reading sequences with reference genome (as which NCBI 37/hg19 assembly was used); 1.3. Variation Caller for identification of genetic variants);

2) ANNOVAR (annotation of the functional value of genetic variants, filtration of known polymorphisms using the GnomAD database);

3) IGV (Integrative Genomic Viewer) for expert filtration of sequencing artifacts and sequence alignment results in which mutations are detected by automatic analysis tools.

To determine the potentially significant variants for each found variant, the occurrence in the investigated group was compared with the occurrence in the sample of 15708 complete genomes of healthy people, separated by NGS method, from the GnomAD database [11]. The p-value was calculated using the continuity corrected χ²-square (Statistica program), FDR correction was used as a multiple test correction.
Measuring of rivaroxaban and dabigatran plasma concentrations

Determination of rivaroxaban and dabigatran plasma concentration was carried out by high-performance liquid chromatography (HPLC) with mass spectrometric detection. Samples were analyzed on the Agilent 1200 liquid chromatograph (consisting of a four-channel pump, mobile phase degasser, chromatographic column thermostat). The Agilent Extend-C18 column (length 100 mm; inner diameter 2.1 mm; grain 3.5 μm) was used. The separation was performed at a column temperature of 40°C. Moving phase: solution “A” (50 ml 0.1 M ammonium acetate solution and 5 ml formic acid solution were diluted with deionized water to a total volume of 1 litre) and solution “B” (50 ml 0.1 M ammonium acetate solution and 5 ml formic acid solution were diluted with acetoneitrile to a total volume of 1 litre).The chromatographic separation was performed in the isocratic elution mode with the ratio of components “A”：“B” 70:30. The flow rate of the mobile phase was 0.3 ml/min. The volume of the introduced sample was 10 μl. The analysis was carried out during 7 min.

We used a mass spectrometer (triple quadrupole type) Agilent Triple Quad LC/MS 6410 with electrospray ionization in positive ionization mode. Registration of rivaroxaban spectra was performed in the mode of multiple molecular reactions. Sprayer gas pressure 35 psi. Drying gas volume speed 11 l/min, temperature 350°C. The value of the fragmentation voltage was 135 V, the voltage in the impact cell was 25 V. The sample preparation was performed by the deposition of plasma proteins. The plasma samples were defrosted at room temperature. Then 100 μl of plasma was transferred to Eppendorf type tubes, 250 μl of methanol mixture with 0.1% hydrochloric acid HCl was added in 9:1 ratio, stirred on Vortex shaker, left for 10 minutes and stirred again. The samples were then centrifuged for 10 min at 10,000 rpm. The supernatant layer was transferred to a chromatographic vial and placed on a chromatograph autosampler.

Results

Dabigatran

In dabigatran group of patients with bleeding events statistically significant deviation from population values was shown by 13 variants of nucleotide sequence (table 2). Among the 11 significant substitutions found for the CES1 gene, 8 (rs3826193, rs761128900, rs3826192, rs3826191, rs3826194, rs2307240, rs62028647, rs74019278, rs76828834) are in the exonic area. At the same
time, 4 of them (rs3826193, rs3826192, rs2307240, rs62028647) lie in the functionally significant area and are non-synonymous (i.e. they lead to the change in amino acid sequence) and 4 (rs3826191, rs3826194, rs74019278, rs76828834) are synonymous (i.e. they do not lead to the change in amino acid sequence). Of the remaining variants of the nucleotide sequence found in the CES1 gene, 2 (rs375970897, rs62028646) belong to the intronic region and 1 to the 5'-nontranslated region (rs761128900). Among the found significant substitutions for the ABCB1 gene, 1 (rs9282564) is in the exonic region and is not synonymous; another 1 (rs41297348) substitution is in the underlying cis-regulating region.

### Rivaroxaban

In patients received rivaroxaban with bleeding events significant deviations showed 7 variants of nucleotide sequence: 4 in ABCG2 gene, 2 in CYP3A4 gene and 1 in ABCB1 gene (Table 3).

Among the 4 significant substitutions found for the ABCG2 gene, one (rs34783571) is in the exonic region and is not synonymous. Of the remaining substitutions for the gene ABCG2, 1 (rs2231157) is in the intronic region and one by one is in the 5'-nontranslated region (rs546230660). The variants showing significant deviations from the population frequencies in the genes ABCB1 (rs531438597) and CYP3A4 (rs55808838) are in the intronic region.

Tables 2 and 3 also show the carrier frequencies of the found variants in the present sample of patients with bleedings on dabigatran or rivaroxaban treatment and in general population. The predictive significance (increased risk of bleeding or protective role) of the found variants will be clarified in future studies on a larger sample of patients with a comparison of the obtained data with patients of similar groups without bleeding.

### Discussion

Patients with bleeding events on DOACs (dabigatran and rivaroxaban) were included in this study. Among patients receiving dabigatran (110 and 220 mg two times a day), only 4 (23.5%) of 17 patients had minimum equilibrium plasma concentrations of the drug exceeding the previously described therapeutic limits [12]. Among patients taking rivaroxaban (10-20 mg once a day), 2 (16.6%) ones had a level of the minimum equilibrium plasma concentration of the drug above the previously described therapeutic limits. The data obtained may indicate that the “gold standard” – assessment of DOAC concentration is not an ideal prognostic factor of bleeding risk for patients taking DOACs; and therefore studies for additional markers of bleeding for dabigatran and rivaroxaban are required.

As mentioned above, dabigatran is a substrate of P-glycoprotein encoded with the ABCB1 gene. In addition, hepatic carboxylesterase-1 (CES1), encoded by the CES1 gene plays an important role in the pharmacokinetics of dabigatran, under the influence of which dabigatran metabolite M2 is converted into the active form of the drug, dabigatran etexilate. [13]. Several polymorphic variants of the CES1 gene

| Gene     | Reference variant | Alternative variant | Substitution type, location | Rs        | Frequency in the studied sample | Frequency in GnomAD |
|----------|-------------------|---------------------|-----------------------------|-----------|---------------------------------|---------------------|
| ABCB1    | A                 | -                   | Intronic                    | rs531438597 | 0,0833                          | 0,0005              |
| ABCG2    | A                 | G                   | On the 3'-non-transmitted area | rs546230660 | 0,0833                          | 0,0003              |
| ABCG2    | C                 | T                   | Exonic, non-synonymous      | rs34783571 | 0,0833                          | 0,0019              |
| ABCG2    | A                 | G                   | Intronic                    | rs2231157  | 0,7500                          | 0,335               |
| ABCG2    | G                 | C                   | On the 5'-non-transmitted area | rs55927234 | 0,0833                          | 0,0026              |
| CYP3A4   | C                 | T                   | Intronic                    | No data available | 0,0833                          | No data available   |
| CYP3A4   | C                 | T                   | Intronic                    | rs55808838 | 0,0833                          | 0,0015              |
associated with lower dabigatran plasma concentrations and lower risk of bleedings have been identified in earlier studies, including full genome association studies [14]. For example, the carriage of minor alleles by the polymorphic marker rs2244613 of the CES1 gene may be associated with lower dabigatran concentrations in plasma and lower risk of bleeding events on dabigatran [14]. Another single-nucleotide polymorphism of the same rs8192935 gene demonstrated association with minimum and maximum dabigatran concentration, but did not affect the risk of bleedings [14,15]. The association with reduction of activation rate of dabigatran is shown also for polymorphic marker rs71647871 of CES1 gene [13]. Single-nucleotide polymorphisms rs4148738, rs1045642 and rs2032582 of the ABCB1 gene, which have been associated with the dabigatran plasma concentration and the risk of bleeding on dabigatran should be highlighted [14,16,17]. At the same time, the variants identified in this study have not been previously described as associated with the risk of bleeding during therapy with dabigatran. This requires investigating the clinical relevance of the identified variants in larger studies. Moreover, the polymorphic variant rs62028647 has shown a strong non-equilibrium linkage with previously well described [18] variant rs2244613, and these variants can be allocated as haplotype.

The polymorphism of ABCB1, ABCG2 genes encoding the efflux transporters, and the polymorphism of CYP3A4 gene encoding the eponymous isoenzyme of cytochrome P-450 system, may have a significant impact on the pharmacokinetics of rivaroxaban and the bleeding risk on rivaroxaban. Previously published studies have described 4 single-nucleotide polymorphisms of the ABCB1 gene (rs2032582, rs1045642, rs4148738, rs1128503), which may be associated (mainly in haplotype) with higher plasma concentrations of rivaroxaban and, consequently, higher risk of bleeding events [17,19,20]. Some allelic single-nucleotide polymorphisms of ABCG2 and CYP3A4 genes, which affect significantly the pharmacokinetic features of rivaroxaban and the risk of bleeding during this treatment, are not described. The polymorphic markers identified in this study for the ABCB1, ABCG2 and CYP3A4 genes were not previously described as associated with the risk of bleeding during rivaroxaban therapy, which also requires an assessment of their clinical significance in larger studies.

Study limitations

The used NGS approach has some technological features; the variants selected according to the NGS results in subsequent studies will be confirmed by classical sequencing using the Senger method after the accumulation of data in larger samples. It should also be noted that the different size of the compared samples introduces additional statistical flaws and errors. Thus, the variants lying at the distribution edges of the smaller sample have a greater representation for their group and, accordingly, may show false significance. This points to the need to confirm the significance of the identified substitutions by comparison with a comparable control sample.

Conclusion

The polymorphic variants of candidate genes ABCB1, ABCG2, CES1, CYP3A4 identified in this study, associated with the risk of bleeding during rivaroxaban or dabigatran treatment, make an important contribution to the pharmacogenetic study of DOACs and require additional assessment of clinical significance in larger studies.

Disclosures. All authors have not disclosed potential conflicts of interest regarding the content of this paper.

Financial support: The study was funded by Russian Science Foundation, project № 16-15-00227
Pharmacogenetic Markers of Bleeding

References

1. Alalwan A.A., Voils S.A., Hartzema A.G. Trends in utilization of warfarin and direct oral anticoagulants in older adult patients with atrial fibrillation. Am J Health Syst Pharm. 2017;74(16):1237-44. DOI:10.2146/ajhp160756.

2. Loo S.Y., Dell’Aniello S., Huiart L., et al. Trends in the prescription of novel oral anticoagulants in UK primary care. Br J Clin Pharmacol. 2017;83(9):2096-106. DOI:10.1111/bcp.13299.

3. Zikas P.D., Kourbeti I.S., Poulou L.S., et al. Medicare part D prescribing for direct oral anticoagulants in the United States: Cost, use and the "rubber effect". PLoS One. 2018;13(6):e0198674. DOI:10.1371/journal.pone.0198674.

4. Philippidis A. Top 15 Best-Selling Drugs of 2018: Sales for most treatments grow year-over-year despite concerns over rising prices. Genetic Engineering & Biotechnology News. 2019 39(4):16-7.

5. Alfirevic A., Downing J., Daras K., et al. Has the introduction of direct oral anticoagulants (DOACs) in England increased emergency admissions for bleeding conditions? A longitudinal ecological study. BMJ Open. 2020;10(5):e033357. DOI:10.1136/bmjopen-2019-033357.

6. Ragia G., Manolopoulos V.G. Pharmacogenomics of anticoagulation therapy: the last 10 years. Pharmacogenomics. 2019;20(16):1113-7. DOI:10.2217/pgs-2019-0149.

7. Kanui S.H., Kreutz R.P. Pharmacogenomics of Novel Direct Oral Anticoagulants: Newly Identified Genes and Genetic Variants. J Pers Med. 2019;9(1):7. DOI:10.3390/jpm9010007.

8. Whirl-Carrillo M., McDonagh E.M., Hebert J.M., et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther. 2012;92(4):414-7. DOI:10.1038/clpt.2012.96.

9. Russian State Registry of Drugs. [cited by Jul 20, 2020]. Available from: https://grls.rosminzdrav.ru/Default.aspx (In Russ.) [Государственный реестр лекарственных средств [цитировано 20.07.2020]. Доступно на: https://grls.rosminzdrav.ru/Default.aspx.

10. Gong I.Y., Kim R.B. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. Can J Cardiol. 2013;29(7 Suppl):S24-S33. DOI:10.1016/j.cjca.2013.04.002.

11. Genome Aggregation Database [cited by Jul 20, 2020]. Available from: https://gnomad.broadinstitute.org.

12. Moner-Banet T., Alberio L., Bart P.A. Does One Dose Really Fit All? On the Monitoring of Direct Oral Anticoagulants: A Review of the Literature. Hamostaseologie. 2020;40(2):184-200. DOI:10.1055/a-1113-0655.

13. Shi J., Wang X., Nguyen J.H., et al. Dabigatran etexilate activation is affected by the CES1 genetic polymorphism G143E (rs71647871) and gender. Biochem Pharmacol. 2016;119:76-84. DOI:10.1016/j.bcp.2016.09.003.

14. Paré G., Eriksson N., Lehr T., et al. Genetic determinants of dabigatran plasma levels and their relation to bleeding. Circulation. 2013;127(13):1404-12. DOI:10.1161/CIRCULATIONAHA.112.001233.

15. Dimatteo C., D’Andrea G., Vecchione G., et al. Pharmacogenetics of dabigatran etexilate: interindividual variability. Thromb Res. 2016;144:1-5. DOI:10.1016/j.thromres.2016.05.025.

16. Sychev D.A., Levanov A.N., Shelekhova T.V., et al. The impact of ABCB1 (rs1045642 and rs4148738) and CES1 (rs2244613) gene polymorphisms on dabigatran equilibrium peak concentration in patients after total knee arthroplasty [published correction appears in Pharmacogenomics Pers Med. 2018 Sep 26;11:167]. Pharmacogenomics Pers Med. 2018;11:127-37. DOI:10.2147/PGPM.S169277.

17. Gouin-Thibault I., Delavenne X., Blanchard A., et al. Interindividual variability in dabigatran and rivaroxaban exposure: contribution of ABCB1 genetic polymorphisms and interaction with clarithromycin. J Thromb Haemost. 2017;15(2):273-83. DOI:10.1111/jth.13577.

18. Sánchez Pascua T. Carboxylesterase 1 genetic variability, expression and potential for drug-drug interactions. Diss. University of Liverpool, 2014 [cited by Jul 20, 2020]. Available from: https://livrepository.liverpool.ac.uk/2006752/1/SanchezTer_Sep2014_2006752.pdf.

19. Lorenzini K.I, Daali Y., Fontana P., et al. Rivaroxaban-Induced Hemorrhage Associated with ABCB1 Genetic Defect. Front Pharmacol. 2016;7:494. DOI:10.3389/fphar.2016.00494.

20. Semessael A.L., Larock A.S., Douxfils J., et al. Rivaroxaban plasma levels in patients admitted for bleeding events: insights from a prospective study. Thromb J. 2018;16:28. DOI:10.1186/s12959-018-0183-3.
Pharmacogenetic Markers of Bleeding

About the Authors:

Karin B. Mirzaev – MD, PhD, Senior Researcher, Head of Department of Personalized Medicine, Research Institute of Molecular and Personalized Medicine; Associate Professor, Chair of Clinical Pharmacology and Therapeutics, Russian Medical Academy of Continuous Professional Education

Dmitriy V. Ivashchenko – MD, PhD, Senior Researcher, Department of Personalized Medicine, Research Institute of Molecular and Personalized Medicine; Associate Professor, Chair of Child Psychiatry and Psychotherapy, Russian Medical Academy of Continuous Professional Education

Ilya V. Volodin – Junior Researcher, Department of Molecular Medicine, Research Institute of Molecular and Personalized Medicine, Russian Medical Academy of Continuous Professional Education; Researcher, Laboratory of Epigenetics, Research Centre for Medical Genetics

Elena A. Grishina – PhD (Biology), Associate Professor, Head of Department of Molecular Medicine, Director of Research Institute of Molecular and Personalized Medicine, Russian Medical Academy of Continuous Professional Education

Kristina A. Akmalova – Researcher, Department of Molecular Medicine, Research Institute of Molecular and Personalized Medicine, Russian Medical Academy of Continuous Professional Education

Anastasia A. Kachanova – Junior Researcher, Department of Molecular Medicine, Research Institute of Molecular and Personalized Medicine, Russian Medical Academy of Continuous Professional Education

Alena A. Skripka – MD, Post-Graduate Student, Chair of Faculty Therapy №1, Sechenov University

Radik M. Minnigulov – MD, Post-Graduate Student, Chair of Clinical Pharmacology and Internal Diseases, Sechenov University

Tatiana E. Morozova – MD, PhD, Professor, Head of Chair of General Medical Practice, Sechenov University

Olga A. Baturina – MD, Post-Graduate Student, Chair of Cardiology, Functional and Sonographic Diagnostics, Sechenov University

Alexander N. Levanov – MD, Assistant, Chair of Occupational Diseases, Hematology and Clinical Pharmacology, Saratov State Medical University named after V.I. Razumovsky

Tatiana V. Shelekhova – MD, PhD, Professor, Head of Chair of Occupational Diseases, Hematology and Clinical Pharmacology, Saratov State Medical University named after V.I. Razumovsky

Alexey I. Kalinink – Researcher, Laboratory of Epigenetics, Research Centre for Medical Genetics

Dmitriy A. Napalkov – MD, PhD, Professor, Chair of Faculty Therapy №1, Sechenov University

Anastasia A. Sokolova – MD, PhD, Associate Professor, Chair of Faculty Therapy №1, Sechenov University

Denis A. Andreev – MD, PhD, Professor, Head of Chair of Cardiology, Functional and Sonographic Diagnostics, Sechenov University

Igor N. Sychev – MD, PhD, Associate Professor, Chair of Clinical Pharmacology and Therapeutics, Russian Medical Academy of Continuous Professional Education

Pavel O. Bochkov – PhD (Biology), Senior Researcher, Department of Personalized Medicine, Research Institute of Molecular and Personalized Medicine, Russian Medical Academy of Continuous Professional Education

Dmitriy A. Sychev – MD, PhD, Professor, Corresponding Member of the Russian Academy of Sciences, Head of Chair of Clinical Pharmacology and Therapeutics, Rector, Russian Medical Academy of Continuous Professional Education