

LOW LEVEL OF RESISTANCE TO ANTICOAGULANT RODENTICIDES IN THE *VKORC1* GENE IN HOUSE MICE (*MUS MUSCULUS*) AND NORWAY RATS (*RATTUS NORVEGICUS*) IN RUSSIA

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Genetic resistance to anticoagulants caused by mutations in the *Vkorc1* gene of the most invasive rodent species – Norway rats and house mice - has not been studied in Russia. We analyzed the variability of the *Vkorc1* gene in house mice and Norway rats in various settlements of Russia, and identified mutations responsible for resistance to rodenticides. Two exons of the *Vkorc1* gene were analyzed in 71 Norway rats from four cities (Moscow, Tyumen, Chita, Rostov-on-Don) and 108 house mice from cities and small settlements (Moscow region, Tormosin, Nizhny Tsasuchei). Three Norway rats (15.8% of the studied individuals) in Moscow have a heterozygous state of the Tyr139Ser mutation, which is responsible for resistance. House mice were not found to have mutations in the *Vkorc1* gene responsible for resistance to anticoagulants of the first and second generation in the Leu128Ser and Tyr139Cys positions located in the third exon. However, in cities, we identified two heterozygous mutations in the first exon have not be described previously in scientific literature: Lys58Arg and Ser31Trp. In Russia, the genetic resistance to rodenticides in settlements in the populations of house mice and Norway rats is significantly lower than in Western Europe.

Key words: invasive species, *Mus musculus*, *Rattus norvegicus*, genetic resistance to anticoagulants; *Vkorc1* polymorphism; Tyr139Ser.

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References

- Boyle C.M. Case of apparent resistance of *Rattus norvegicus* Berkenhout to anticoagulant poisons // Nature. 1960. Vol. 188. № 4749. P. 517-517.
- Buckle A. P. Anticoagulant resistance in the United Kingdom and a new guideline for the management of resistant infestations of Norway rats (*Rattus norvegicus* Berk.) // Pest Manag Sci. 2013. Vol. 69. № 3. P. 334–341.
- Buckle A., Endepols S., Klemann N., Jacob J. Resistance testing and the effectiveness of difenacoum against Norway rats (*Rattus norvegicus*) in a tyrosine139cysteine focus of anticoagulant resistance, Westphalia, Germany // Pest Manag Sci. 2013. Vol. 69. № 2. P. 233–239.
- Buckle A., Jones C., Talavera M., Prescott C. Anticoagulant Resistance in Rats and Mice in the UK - Summary Report with new data for 2019-20 Report from the Campaign for Responsible Rodenticide Use (CRRU) UK for the Government Oversight Group. Vertebrate Pests Unit, University of Reading, UK, 2020. 19 pp. <https://www.thinkwildlife.org/> (accessed: 06.10.20).
- Capizzi D., Bertolini S., Mortelliti A. Rating the rat: global patterns and research priorities in impacts and management of rodent pests // Mammal Rev. 2014. Vol. 44. № 2. P. 148–162.
- Dodsworth E. Mice are spreading despite such poisons as warfarin // Munic Eng London. 1961. Vol. 3746. P. 1668-1668.

- Duncan B.J.M.L., Koenders A., Burnham Q., Lohr M.T. *Mus musculus* populations in Western Australia lack VKORC1 mutations conferring resistance to first generation anticoagulant rodenticides: Implications for conservation and biosecurity // PLoS One. 2020. Vol. 9:e0236234. // <https://doi.org/10.1371/journal.pone.0236234>.
- Endepols S., Buckle A., Eason C., Pelz H.J., Meyer A., Berry P. et al. RRAC guidelines on anticoagulant rodenticide resistance management // Technical Report. Croplife International, Brussels. 2015. P. 1–30.
- Espinosa M.B. Efficacy of anticoagulant drugs as rodenticides and genetic variation on *Vkorc1* of *Mus musculus* from Buenos Aires province (Argentina) // J of Basic and Applied Gen. 2013. Vol. 24. № 1. P. 27–31.
- Goulois J., Lambert V., Legros L., Benoit E., Lattard V. Adaptive evolution of the *Vkorc1* gene in *Mus musculus domesticus* is influenced by the selective pressure of anticoagulant rodenticides // Ecol Evol. 2017. Vol. 7. №8. P. 2767–2776.
- Hall T.A. BioEdit: a user-friendly biological sequence alignment editor and analysis program for Windows 95/98/NT // Nucleic Acids Res. 1999. Vol. 41. P. 95–98.
- Haniza M.Z., Adams S., Jones E.P., MacNicoll A., Mallon E.B., Smith R.H., Lambert M.S. Large-scale structure of brown rat (*Rattus norvegicus*) populations in England: effects on rodenticide resistance // Peer J. 2015. Vol. 3:e1458.
- Iannucci A., Natali C., Capizzi D., Sinibaldi I., Sposimo P., Ciofi C., Fratini. S. First record of VKORC1 sequence mutation associated with resistance to anticoagulant rodenticides in Italian individuals of *Mus musculus domesticus* // Hystrix – It J Mamm. 2019. Vol. 30. P. 183–185.
- Jones C., Talavera M., Buckle A., Prescott C. Anticoagulant Resistance in Rats and Mice in the UK – Summary Report with new data for 2019. Report from the Campaign for Responsible Rodenticide Use (CRRU) UK for the Government Oversight Group. Vertebrate Pests Unit, University of Reading, UK. 2019. 30 pp. https://www.thinkwildlife.org/downloads_resources/ [accessed: 18.09.20].
- Korobitsina K.B., Yakimenko L.V. The role and place of wagneri-like forms of house mouse (Rodentia, Muridae) in the fauna of Russia and adjacent countries // Zool Zh. 2004. Vol. 83. P. 1081–1030. (In Russian with English summary).
- Kumar S., Stecher G., Li M., Knyaz C., Tamura K. MEGA X: Molecular evolutionary genetics analysis across computing platforms // Mol Biol Evol. 2018. Vol. 35. P. 1547–1549.
- Li T., Chang C.Y., Jin D.Y., Lin P.J., Khvorova A., Stafford D.W. Identification of the gene for vitamin K epoxide reductase // Nature. 2004. Vol. 427. P. 541–544.
- Ma X., Wang D., Li N., Liu L., Tian L., Luo C. et al. Low warfarin resistance frequency in Norway rats in two cities in China after 30 years of usage of anticoagulant rodenticides // Pest Manag Sci. 2018. Vol. 74. № 11. P. 2555–2560.
- Maltsev A.N., Stakheev V.V., Bogdanov A.S., Fomina E.S., Kotenkova E.V. Phylogenetic relationships of intraspecific forms of the house mouse *Mus musculus*: Analysis of variability of the control region (D-loop) of mitochondrial DNA // Dokl Biol Sci. 2015. Vol. 465. №3. P. 285–288.
- Maltsev A.N., Stakheev V.V., Kotenkova E.V. Role of invasions in formation of phylogeographic structure of house mouse (*Mus musculus*) in some areas of Russia and the near abroad // Russ J Biol Invasions. 2016. Vol. 7. №2. P. 255–267.
- McGee C.F., McGilloway D.A., Buckle A.P. Anticoagulant rodenticides and resistance development in rodent pest species – A comprehensive review // J Stored Prod Res. 2020. Vol. 88. № 101688. P. 1–18.
- Meerburg B.G., Van Gent-Pelzer M.P., Schoelitz B., Esther A., Van der Lee T.A. Distribution of anticoagulant rodenticide resistance in *Rattus norvegicus* in the Netherlands according to *Vkorc1* mutations // Pest Manag Sci. 2014. Vol. 70. № 11. P. 1761–1766.
- Mironova T.A., Rylnikov V.A., Bogacheva A.V., Lavrenchenko L.A. Distribution of VKORC1 gene mutations and resistance of gray rats to anticoagulant rodenticides in a number of Russian cities // Pest Management. 2020. Vol. 1. P. 5–7. (In Russian with English summary).
- Mooney J., Lynch M.R., Prescott C.V., Clegg T., Loughlin M., Hannon B. et al. VKORC1 sequence variants associated with resistance to anticoagulant rodenticides in Irish populations of *Rattus norvegicus* and *Mus musculus domesticus* // Sci Rep. 2018. Vol. 8. № 4535. DOI:10.1038/s41598-018-22815-7.
- OEPP/EPPO EPPO Standard PP 2/1(1). Guideline on good plant protection practice: principles of good plant protection practice // OEPP/EPPO Bulletin. 1994. Vol. 24. P. 233–240.
- Oldenburg J., Marinova M., Müllerreible C., Watzka M., The vitamin K cycle // Vitam Horm. 2008. Vol. 78. P. 35–62.
- Pelz H.J., Rost S., Hunerberg M., Fregin A., Heiberg A.C., Baert K. et al. The genetic basis of resistance to anticoagulants in rodents // Genetics. 2005. Vol. 170. № 4. P. 1839–1847.
- Pelz H.J., Rost S., Müller E., Esther A., Ulrich R.G., Müller C.R. Distribution and frequency of *Vkorc1* sequence variants conferring resistance to anticoagulants in *Mus musculus* // Pest Manag Sci. 2012. Vol. 68. P. 254–259.
- Petrosyan V.G., Khlyap L.A. The most dangerous invasive species in Russia (TOP-100) / Eds. Yu.Yu. Dgebuadze, M.: KMK Scientific Press Ltd, 2018. 688 p. (In Russian with English summary).
- Pocock M.J., Searle J.B., White P.C. Adaptations of animals to commensal habitats: population dynamics of house mice *Mus musculus domesticus* on farms // J Anim Ecol. 2004. Vol. 73. №5. P. 878–888.
- Prager E.M., Tichy H., Sage R.D. Mitochondrial DNA sequence variation in the eastern house mouse, *Mus musculus*: comparison with other house mice and report of a 75-bp tandem repeat // Genetics. 1996. Vol. 143. P. 427–446.
- Prescott C., Resistance to the anticoagulant rodenticides – the deployment of the new molecular methodology to identify mutations of the VKORC1 resistance gene,

- and understanding their potential impact on treatment outcome // Pest Management. 2013. T.88. №4. C. 39-46. (In Russian with English summary).
- Prescott C.V., Buckle A.P., Gibbings J.G., Allan Ed N.W., Stuart A.M. Anticoagulant resistance in Norway rats (*Rattus norvegicus* Berk.) in Kent – a VKORC1 single nucleotide polymorphism, tyrosine139phenylalanine, new to the UK // Intl J Pest Management. 2010. Vol. 57. №1. P. 61–65.
- Rost S., Fregin A., Ivaskevicius V., Conzelmann E., Hörtnergel K., Pelz H.J., Lappégard K., Seifried E., Scharrer I., Tuddenham E.G., Müller C.R., Strom T.M., Oldenburg J., Mutations in *VKORC1* cause warfarin resistance and multiple coagulation factor deficiency type 2 // Nature. 2004. Vol. 427. № 6974. P. 537–541.
- Rost S., Pelz H.J., Menzel S., Conzelmann E., MacNicoll A.D., León V., Song K.J., Jäkel T., Oldenburg J., Müller C.R. Novel mutations in the VKORC1 gene of wild rats and mice—a response to 50 years of selection pressure by warfarin? // BMC Genet. 2009. V. 10. №1. P. 1-9.
- Spiridonova L.N., Introgression of nuclear and mitochondrial DNA markers of *Mus musculus musculus* to aboriginal populations of wild mice from Central Asia (*M. m. wagneri*) and South Siberia (*M. m. gansuensis*) // Mol Biol. 2014. Vol. 48. P.75–83.
- Unified register of certificates of state registration in the Russian Federation, 2020 (<https://portal.eaeunion.org>).