Trends in **Molecular Biology** • Special issue

Abstract Book

CoMBoS2

2nd Congress of Molecular Biologist of Serbia

ISBN-978-86-82679-15-8

Belgrade • 2023

CoMBoS2 – the Second Congress of Molecular Biologists of Serbia, Abstract Book – Trends in Molecular Biology, Special issue
06-08 October 2023, Belgrade, Serbia
Online Edition
https://www.imgge.bg.ac.rs/lat/o-nama/kapacitet-i-oprema/istrazivacka-delatnost
https://indico.bio.bg.ac.rs/e/CoMBoS2

IMPRESSUM

PUBLISHER:
Institute of Molecular Genetics and Genetic Engineering (IMGGE), University of Belgrade

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Institute of Molecular Genetics and Genetic Engineering (IMGGE),
University of Belgrade
Belgrade, 2023
ISBN 978-86-7078-173-3

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Content

MOLECULAR BASIS OF PHENYLKETONURIA IN SERBIA: AN UPDATE

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Introduction: Phenylketonuria (PKU) is the most frequent inborn disorder of amino acid metabolism caused by variants in human phenylalanine hydroxylase gene (*PAH*).

Methods: In this study (an update for the time period of 10 years, with patients from our previous studies included) a total of 109 PKU patients from Serbia were analyzed. They were classified into three phenotypic categories in accordance with pre-treatment plasma phenylalanine level: classic PKU, mild PKU and mild hyperphenylalaninemia. For genetic analyses, we combined Sanger sequencing, MLPA and next generation sequencing to identify disease-causing variants in *PAH* gene, which were further classified using ACMG classification. Additionally, we used *in silico* and/or eukaryotic expression studies to assess the effect of novel genetic variants identified in our patients.

Results: Disease-causing variants were identified in 217 of 218 alleles, reaching detection rate of 99.5%. We detected a total of 32 different variants, of which 29 previously described and three novel ones: p.Gln226Lys, p.Pro244His and p.Pro416Leu. *In silico* and/or eukaryotic expression studies confirmed pathogenic effect of all novel genetic variants. The most frequent variant was p.Leu48Ser (31.2%), followed by p.Arg408Trp (13.8%), p.Ile306Val (9.2%). p.Glu390Gly (5%), p.Pro281Leu (4.6%), and p.Arg261Gln (3.2%). All detected disease-causing variants were classified as pathogenic using ACMG classification.

Conclusion: Our study brings the updated spectrum of molecular genetic data, variant classification and detailed phenotypic characteristics for PKU patients from Serbia. Therefore, our study contributes to better understanding of molecular landscape of PKU in Europe and to general knowledge on genotype–phenotype correlation in PKU.

Key words: phenylketonuria; phenylalanine hydroxylase; variant; genotype-phenotype correlation

Acknowledgements: This study was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Agreement no. 451-03-47/2023-01/200042).