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Content

RARE METABOLIC DISEASES IN THE GENOMICS ERA

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Introduction: All inborn metabolic diseases are rare, having a prevalence less than 1:2000. Vast majority of them are monogenic and finding pathogenic genetic variants is needed to set the correct diagnosis, enable adequate treatment and provide genetic counseling to members of affected family. This study is an overview of genomic studies of rare metabolic diseases in Serbia.

Methods: Since 2005, more than 300 patients suspected to have a rare metabolic or neurometabolic disease have been analyzed using sanger sequencing, clinical-exome sequencing, whole-exome sequencing or whole-genome sequencing in order to find disease-causing or disease-modifying variants. Novel variants were characterized using *in silico* modelling or in *in vitro* eukaryotic assays (standard or CRISPR/Cas9 developed).

Results: Disease-causing variants were found in more than 60 different genes associated with a metabolic or neurometabolic disease. The most frequent disease was phenylketonuria (109 patients), followed by glycogen storage disease Ib (30 patients), while majority of diseases is seen only in a single patient. More than 40 new genetic variants were comprehensively characterized *in silico* or *in vitro*. For the first time, candidate modifiers (*SHANK* gene family) were identified in a group of phenylketonuria patients with an unusual phenotype.

Conclusion: In the genomics era, next-generation sequencing significantly shortens time to diagnosis and allows studying genetic modifiers of monogenic diseases and genotype-phenotype correlation. Furthermore, characterization of novel genetic targets boosts development of precision medicine.

Key words: rare diseases; next-generation sequencing; genomics; precision medicine

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