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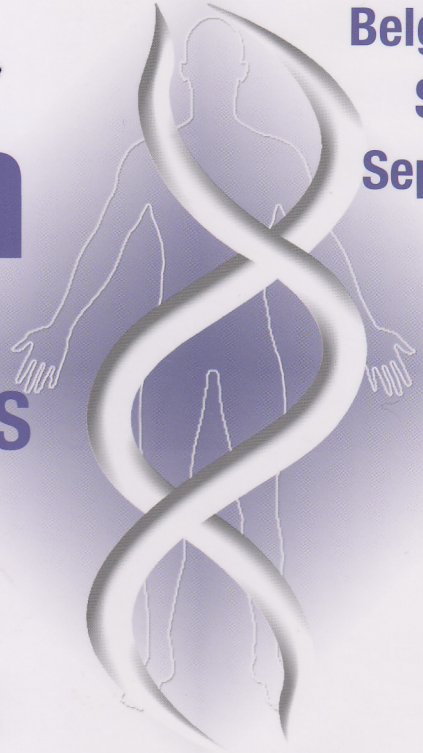
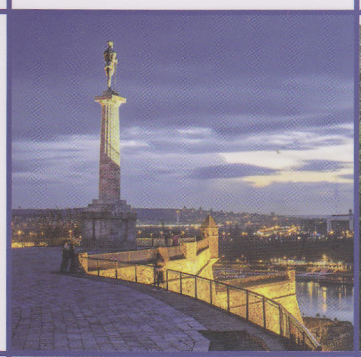
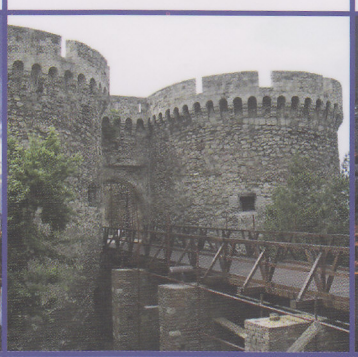
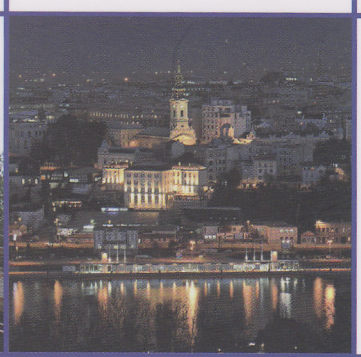


SERBIAN GENETIC SOCIETY


This is the first previously unreported *PAH* mutation in Serbian population. It was concluded that p.Gln226Lys is a disease causing mutation, and it does not respond to BH4. Therefore, our study contributes to functional landscape of *PAH* mutations and personalized medicine in PKU.

Keywords: phenylketonuria, PAH gene, mutation, BH4

GENOTYPE-PHENOTYPE CORRELATION IN THE SERBIAN PATIENTS WITH CLASSICAL FORM OF CONGENITAL ADRENAL HYPERPLASIA

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Background: Congenital adrenal hyperplasia (CAH) is a monogenic autosomal recessive condition manifested as a heterogeneous phenotype. Classical CAH can present as severe salt wasting (SW) or simple virilizing (SV) form. It is caused by mutations in the CYP21A2 gene on chromosome 6p21.3. Nine pseudogene-derived CYP21A2 point mutations account for about 80% of all CYP21A2 defects.

Methods: Using the PCR/ACRS method, we have analyzed nine most common CYP21A2 point mutations in 11 Serbian patients with the classical form of CAH diagnosed according to the standard clinical criteria at the Institute for Mother and Child Health, Belgrade, Serbia. Molecular analysis was performed in the Genetic Laboratory at the University Children's Clinic, Skopje, Republic of Macedonia. Of the patients 6 had SW and 5 had SV form of the disease.

Results: In 9/11 (81.8%) of the patients five of the analysed mutations were detected. In 5/6 SW patients the following genotypes were detected: IVS2/IVS2 in 2 patients, IVS2/Q318X, IVS2/R356W and P30L/P30L+IVS2 in one patient each. Genotype-phenotype correlation was observed in 80% of the SW patients. In 4/5 SV patients the following genotypes were detected: IVS2/P30L in 2 patients, I172N/I172N and P30L/P30L in the one patient each. Genotype-phenotype correlation was observed in 75% of the SV patients. Our finding supports the role of the P30L mutation in pronounced virilization.

Conclusion: Although correlation between genotype and phenotype in the CAH patients is considerable, our results showed that there is genotype-phenotype discordances and genotype cannot be always predictive of phenotype.

Keywords: classical congenital adrenal hyperplasia; CYP21A2 gene; point mutations; genotype-phenotype correlation

ABSENCE OF *NBS1657DEL5* AND *TP53 EXON8* MUTATIONS IN SERBIAN *BRCA1/2* NEGATIVE HEREDITARY BREAST/OVARIAN CANCER

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Introduction: Although hereditary breast cancer usually arises as the consequence of *BRCA1/2* deleterious mutations, a large portion of hereditary susceptibility still remains unexplained. Under the polygenic model of inheritance, *TP53* and *NBS1* were shown to contribute to hereditary breast cancer. *NBS1* 657Del5 mutation increases the risk for breast cancer three times while mutations in *TP53* exon 8 increase the risk for early-onset breast cancer. Since mutations in *BRCA1/2* can't explain the whole range of hereditary predisposition, we aimed to investigate the presence of *NBS1* 657del5 and *TP53* exon 8 mutations in hereditary breast cancer in Serbia.

Methods and Results: 57 subjects from high-risk families negative for mutations in *BRCA1/2* genes were included in this study. All of them were screened for the presence of *NBS1* 657del5 mutation. 21 of them (≤40 years) were selected for *TP53* exon 8 mutation detection. Mutation detection was done by High Resolution Melting Analysis on Roche Light Cycler. All profiles that deviated from the control samples were sequenced. The investigated group of patients was negative for 657del5 mutation in *NBS1* gene. Young breast cancer patients (≤40 years) showed no alterations in the exon 8 of *TP53* gene.

Conclusions: The absence of *TP53* and *NBS1* mutations in the selected groups of patients indicates that deleterious mutations in other breast cancer susceptibility genes may account for the increased susceptibility in our cohort of high-risk *BRCA1/2* negative cases. This result encourages further examination on different genes that may significantly contribute to the disease predisposition in Serbia.

Keywords: NBS1, TP53, mutations, hereditary breast cancer

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EVALUATION OF POTENTIAL APPLICATION OF ANTISENSE THERAPY IN DUCHENNE MUSCULAR DYSTROPHY PATIENTS IN BOSNIA AND HERZEGOVINA

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Duchenne muscular dystrophy is progressive neuromuscular disorder, caused by mutation in DMD (dystrophin) gene. Mutations in this gene result in prematurely truncated or nonfunctional dystrophins. This disorder affects one in 3500 newborn boys, since it is X-linked recessive disorder. New therapeutic application for Duchenne muscular dystrophy includes antisense-mediated exon skipping which aims for reading frame restoration. This method uses synthetic antisense oligonucleotides, which are targeted to specific regions of pre-mRNA transcripts, to modulate splicing of pre-mRNA, which causes skipping of specific exon. Internally deleted dystrophins have partial functionality, as shown in Becker muscular dystrophy, which is less severe phenotype that Duchenne muscular dystrophy. Exon skipping is based on premise that severity of phenotype can be restored to less severe, by introducing a production of partly functional instead of nonfunctional dystrophin in Duchenne muscular dystrophy patients.

During the period of 2012-2014, there were 14 Duchenne muscular dystrophy patients referred to genetic testing for DMD mutations in Laboratory for human genetics, Institute for genetic engineering and biotechnology by neuropediatricians and medical geneticist. To evaluate potential application of antisense therapy in these patients, we had to cross-check every mutation in DMD mutation database. It was found that majority of confirmed Duchenne muscular dystrophy patients (67%) had deletions of exons 45-52, respectively, one patient has duplication of exon 2, and the rest of patients had mutations in exons 1-23. Theoretically, great majority of the patients from our database (92%), might benefit from novel treatment approach - antisense therapy.

Keywords: DMD, antisense therapy, exon skipping

ASSOCIATION OF SINGLE NUCLEOTIDE POLYMPRPHISM IN PLATELET GLYCOPROTEIN RECEPTOR GPIa WITH DIABETIC RETINOPATHY IN PATIENTS WITH TYPE 2 DIABETES

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Studies have shown that platelets might be involved in the pathogenesis of diabetic microangiopathy. The platelet membrane glycoprotein complex (GP) Ia/IIa is a major collagen receptor. Linked polymorphisms within the coding region of the GPIa gene (C807T and G873A) were identified and related to GPIa/IIa surface expression. The T807/A873 allele is associated with higher expression of this receptor. This polymorphism creates restriction site for Bgl