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Poszukiwanie nowych zmienności genetycznych u pacjentów z rodzinnymi parkinsonizmami w populacji polskiej.

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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III. Streszczenie w języku angielskim

Title: **Novel genetic variants associated with familial forms of parkinsonism in Polish population.**

Introduction

PD is one of the most common neurodegenerative movement disorders in the world, affecting people of all ethnicities. Most cases of PD are sporadic; however, about 15% are familial forms. The genetic cause of PD is usually identified in patients with an early onset of symptoms or in those with a positive family history. The aim of the series of publications is to analyze the genetic variation associated with parkinsonism in the Polish population.

Methodology

In the review paper, the electronic database, PubMed, was searched. The *SNCA* duplication was revealed with MLPA-MRC-Holland kit usage. In the study analyzing a family with a *TOR1A* mutation, whole-exome sequencing was performed using the Illumina Novaseq 6000 platform. To confirm the presence of the variant, Sanger sequencing of the *TOR1A* was conducted in the proband. In the Perry syndrome paper, Sanger sequencing of *DCTN1*, exon 2 was performed. In the third study, Sanger sequencing of *PRKN, PINK1, DJ1* and the exome rearrangements analysis with MLPA MRC-Holland kit usage were carried .

Results

The review paper summarizes the current knowledge in the genetic studies conducted in Polish PD patients.

The first original article showed the presence of the p. (Glu121Lys) mutation in the TOR1A gene in proband. There were no other mutations in 23 previously described PD-related OMIM genes. The available databases were analyzed - this variant was revealed in 3 patients from the NHLBI database (0.02%) and in 0.03% of patients from the gnomAD database. Additionally, the database of 600 WES results from the Department of Medical Genetics of the Institute of Mother and Child revealed this variant in 2 healthy men (0.33%).

The second publication described the clinical and neuropsychological characteristics of two Perry syndrome families- Polish and Colombian. In the Polish family, eleven years of

observation revealed that the dominant neuropsychological phenotype was the behavioral variant of frontotemporal dementia.

In the third study, 541 EOPD patients were included (Czech Republic n = 11, Germany n = 38, Poland n = 476, Ukraine n = 16). Among all patients, 17.2% (n = 93) had a positive family history. In the Polish population, a positive family history was found in 15.8% of patients (n = 75). Fourteen Polish patients had a homozygous or complex heterozygous mutation in *PRKN* and 3 patients had homozygous mutations in the *PINK1*. The PRKN p.Glu79Ter and p.Cys466Phe variants have not been previously reported in other populations in the available databases.

Conclusions

To sum up, in the Polish population there may occur genetic variants characteristic for familial parkinsonism. The identification of specific variants in known genes is the first step to new parkinsonism's loci discovery in the future.