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Original scientific article

ANALYSIS OF "CLINICAL EXOME" PANEL IN SERBIAN PATIENTS WITH COGNITIVE DISORDERS

Marija BRANKOVIĆ[1,2], Elka STEFANOVA[1,2] , Gorana MANDIĆ[1,2], Ana MARJANOVIĆ[1,2], Valerija DOBRIČIĆ[3], Aleš MAVER[4], Gaber BERGANT[4], Zorica STEVIĆ[1], Milena JANKOVIĆ[1], Ivana NOVAKOVIĆ[2], Borut PETERLIN[4], Vladimir KOSTIĆ[1,2]

[1]Neurology Clinic, University Clinical Center of Serbia, Belgrade, Serbia
[2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[3]Luebeck Interdisciplinary Platform for Genome Analytics (LIGA), University of Luebeck, Luebeck, Germany
[4]Clinical Institute of Medical Genetics, University Medical Centre Ljubljana, Ljubljana, Slovenia

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As life span rises, dementia has become a growing public health issue. According to current estimates, almost 50 million people worldwide have dementia, and the number is expected to grow. Next generation sequencing (NGS) methods have helped significantly with identifying causative gene variants related to various cognitive disorders. Our study aimed to analyze the genetic basis of cognitive disorders using NGS clinical exome panel. The study included a total number of 15 unrelated cases diagnosed with cognitive disorders, all negative after standard targeted genetic testing was performed (available at Neurology Clinic, UCCS, Belgrade, Serbia). Preference was given to familial cases with early presentation or complex phenotype. Sequencing of a clinical exome (CE) panel for 4813 genes with known associated clinical phenotypes was performed using TruSight One sequencing panel on an Illumina MiSeq NGS platform according to the manufacturer's instructions (Illumina, San Diego, CA, USA). Variants were analyzed with Illumina Variant Studio v3 software provided by Illumina as well as a previously developed pipeline. Variants analysis and interpretation were based on phenotype gene target approach, literature and databases search, allele frequency, and pathogenicity prediction by *in silico* software. All causative variants were confirmed by Sanger sequencing. Whenever possible, additional family members were studied for segregation analysis. CE panel analysis revealed a likely genetic cause in four patients. We have

Corresponding author: Marija Branković, Neurology Clinic, University Clinical Center of Serbia, dr Subotića starijeg 6, 11000 Belgrade, Serbia, Phone:+381112658355,e-mail: mara.brankovic@gmail.com

detected two missense heterozygous pathogenic variants in the *PSEN1* gene in one patient each and homozygous nonsense pathogenic variant in the *OPTN* gene in two more patients. Detected pathogenic variants are in line with the clinical phenotype of our patients. In the rest of the 11 cases, genetic diagnosis remains unclear. The results of our study emphasize the significance of CE panel analysis in establishing a diagnosis for patients with dementia. Furthermore, give us insight into the complexity of the genetic background of this group of disorders.

Key words: cognitive impairments, DNA diagnostics, gene panels, gene variant, *PSEN1, OPTN*

INTRODUCTION

Dementia is a syndrome characterized by a progressive, acquired decline in cognitive functioning caused by degeneration of the nervous system (PRINCE *et al*., 2013). In recent years it has been estimated that around 55 million people worldwide were living with dementia (GAUTHIER *et al*., 2021), and the number of new cases is expected to increase in the future. In Serbia the number of people living with dementia is estimated to be 13.58 cases per 100000 (https://www.worldlifeexpectancy.com/cause-of-death/alzheimers-dementia/by-country/ accessed on July 2022).

Cognitive disorders include mild and severe cognitive impairment (known as dementia) (SACHS-ERICSSON and BLAZER, 2015). Mild cognitive impairment (MCI) is considered a transitional period between normal age-related cognitive decline and dementia (ANDERSON, 2019).

Alzheimer's disease (AD) represents the most common cause of dementia (PRINCE *et al*., 2013, LOBO *et al*., 2000; CHAN *et al*., 2013) and is characterized by impairment in episodic memory, visuospatial, language, and executive domains (APOSTOLOVA, 2016). Pathological variants in the APP**,** PSEN1, and PSEN2 genes represent the major cause of early-onset Mendelian AD (EOAD) cases. In more detail, around 15% of cases are caused by pathological variants in *APP*, 80% in *PSEN1*, while only 5% by variants in the *PSEN2* gene (HINZ and GESCHWIND, 2017). Considering late onset AD (LOAD), the apolipoprotein E gene (APOE) allele ε4 is the most know genetic factor associated with an increased risk (SAUNDERS *et al*., 1993; CACACE *et al*., 2016). However, numerous genetic mechanisms at the root of AD have yet to be clarified.

Frontotemporal dementia (FTD) is the second most common form of dementia in patients aged 65 and younger (JARMOLOWICZ *et al*., 2015; SMITS *et al*., 2015). FTD is commonly presented with behavioural changes, and/or language deficits, and frontal executive deficits (RASCOVSKY *et al*., 2007; SEELAAR *et al*., 2011; GRAFF-RADFORD and WOODRUFF, 2007).

Clinical subtypes of FTD are divided into behavioural variant (bvFTD) (RASCOVSKY *et al*., 2011), an agrammatic variant of a primary progressive aphasia (agPPA) (OGAR *et al*., 2007; GORNO-TEMPINI *et al*., 2011; GROSSMAN, 2012), and a semantic variant of primary progressive aphasia (svPPA) (HODGES *et al*., 1992; GORGO-TEMPINI *et al*., 2011). About 30% of all FTD cases are genetically caused by pathological variant in one of three genes: C9ORF72**,** MAPT or GRN **(**GREAVES and ROHRER 2019; MAHONEY *et al*., 2012; SNOWDEN *et al*., 2012**).** Pathological variants in each of these genes effect between ~ 5 and 10%

of all FTD cases, with different geographical distribution. Overall, C9ORF72 seems to be the most common genetic cause of FTD worldwide, followed by GRN, and then MAPT **(**BORRONI *et al*., 2011; BARANDIARANE *et al*., 2012**).** Furthermore, causative variants in many other genes associated with FTD have been found, too, albeit in rare cases (SIEBEN *et al*., 2012). In recent years, clinical, pathological, and genetic studies have been supporting the fact that FTD and amyotrophic lateral sclerosis (ALS) are part of a disease spectrum with common underlying pathogenesis (BENNION-CALLISTER and PICKERING-BROWN, 2014; HARDY and ROGAEVA, 2014). ALS-causing mutations can manifest as FTD, sometimes in the same family or even the patient (ALS/FTD comorbidity) (FREISCHMIDT *et al*., 2015; DOLS-ICARDO *et al*., 2018; POTTIER *et al*., 2018).

Dementias could be presented with a complex phenotype that makes a selection of suitable genetic tests laborious. Therefore, sometimes is necessary to perform many different genetic tests to establish an accurate diagnosis.

The development of the next generation of sequencing (NGS), which evaluates many genes simultaneously, and its wide availability of different approaches revolutionized clinical genetic testing. Nowadays, a smaller panel of genes, a whole exome (WES) or a whole-genome (WGS), can be analyzed.

In practice, due to the high cost, WES/WGS is still not available for small genetic centres with limited resources, so smaller gene panels are used as an alternative approach (REALE *et al*., 2018; MONTAUT *et al*., 2018).

Clinical exome (CE) panel covers 4813 genes associated with human diseases and has been used in clinical practice worldwide (OKAZAKI *et al*., 2016; PAJUSALU *et al*., 2018). Using CE panel, single nucleotide variants (SNVs) and small insertions and deletions can be detected in genomic DNA. So far, numerous studies using CE panel for analysis of various monogenic disorders, including dementia, have been conducted (BONVICINI *et al*., 2019; ZALAR *et al*., 2018).

In our study, we intend to analyze the genetic background of 15 patients suffering from different types of dementias in the Serbian population using the CE diagnostic panel. We also aimed to determine the distribution and spectrum of pathogenic variants in genes related to dementias.

MATERIALS AND METHODS

Study subjects

This study included a total number of 15 unrelated patients clinically diagnosed with various cognitive disorders. More specifically, we analyzed 8 cases of early-onset Alzheimer's disease, 6 cases of frontotemporal dementia, and 1 case of mild cognitive impairment. A clinical diagnosis has been made based on the clinical presentation of the disease, and detailed neurological, imaging, and laboratory investigations. For each patient, the family history was determined based on the Goldman score (GOLDMAN *et al*., 2005). In respondents selection, preference was given to patients that fulfill some of the following requirements: patients negative after standard (routine) genetic tests available at Neurology clinic, UCCS, Belgrade, Serbia, cases with a positive family history of the disease, with early onset clinical signs or complex phenotype, suggestive genetic heterogeneity or combination of multiple syndromes. Additionally, for each proband carrying possible disease causing gene variant, affected relatives

were included in the analysis, if available. The control group consisted of 200 healthy people from the population of Serbia.

Each respondent or designated guardian provided written informed consent for participation in the study and publication of the results. The study was approved by the ethics committee of the Clinical Center of Serbia, Belgrade, Serbia (No.:402/6, from 01/30/20).

DNA extraction

Genomic DNA was extracted from 5 ml peripheral blood samples using the salting-out method (MILLER *et al*., 1988).

CE library preparation and sequencing

Sequencing of clinical exome (CES), including coding regions with boundary intron sequences of 4813 clinically relevant genes, was performed using the TruSight One Panel on the Illumina MiSeq NGS platform (Illumina, San Diego, CA). DNA libraries were prepared in groups of three patients according to the manufacturer's protocol using Reagent Kit V3 (Illumina, San Diego, CA). Library quantity and quality were determined by Qubit® 3.0 Fluorimeter with the Qubit™ dsDNA HS Assay Kit (Thermo Fisher Scientific, MA, USA). The average library size was determined using Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA). A paired-end sequencing reaction in 150 cycles was conducted on the Illumina MiSeq platform (Illumina, San Diego, CA).

Data analysis and interpretation

The NGS data analysis was done as previously described in detail (BRANKOVIC *et al.*, 2022) using Illumina Variant Studio V3 software and an in-house analysis pipeline developed by MAVER *et al*., (2016) and BERGANT *et al*., (2018) based on the bwa-GATK platform (DEPRISTO *et al*., 2011). Based on the patient's symptoms, we made virtual gene subpanels using Human Phenotype Ontology (HPO) (KÖHLER *et al*., 2021) (https://hpo.jax.org/app/) for each patient (MAVER *et al*., 2016).

For detected variants, the frequency estimation in the general population was based on the information from the GnomAD project (KARCZEWSKI *et al*., 2021).

The variants considered as significant were: with convincing sequencing quality (≥10 reads for homozygous and ≥20 reads for heterozygous) occurring in genes consistent with the phenotype, variants with frequency ≤1% in our and global population, classified as pathogenic and/or likely pathogenic in ClinVar (LANDRUM *et al*., 2018), HGMD (STENSON *et al*., 2003), and LOVD (FOKKEMA *et al*., 2011) databases of genomic variants, or in the published literature, with functional studies obtained. Fitting with the known model of inheritance was also required to confirm pathogenicity. For variants that have not been reported previously in databases or literature, we performed predictive *in silico* analysis using CADD (RENTZSCH *et al*., 2021), MutationTaster (SCHWARZ *et al*., 2010), MetaLR, and REVEL software. Additionally, we used the PolyPhen tool (ADZHUBEI *et al*., 2010) to estimate the possible impact of an amino acid substitution on the structure and function of a human protein. All considered variants were classified following the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) standards and guidelines (RICHARDS **et al**.,

2015). Significant variants identified in this study have been submitted to the ClinVar database (LANDRUM *et al*., 2018) (submission numbers are provided in Table 1).

Confirmation, family members, controls

Detected potentially disease causing variants were validated by direct Sanger sequencing on the Applied Biosystems 3500 Genetic Analyzer (Applied Biosystems, CA, USA). The samples were prepared using BigDye Terminator v.3.1 cycle sequencing kit (Applied Biosystems, CA, USA), while generated nucleotide sequences were analyzed with Sequencher 4.10.1 Demo software (Gene Codes Corporation, USA).

After confirmation of NGS results in probands, direct targeted Sanger sequencing was performed in family members' samples (if available) for segregation analysis. Sanger sequencing was also performed in 200 healthy Serbian controls to estimate the frequency of potentially causative variants in this population.

RESULTS

Using CES analysis for detecting simple genetic variants in coding regions of the 4813 clinically relevant genes, we identified a likely genetic cause in 4 out of 15 unrelated cases of dementia, representing a diagnostic yield of 26.7%. All detected variants were confirmed in probands by Sanger sequencing.

We have identified two missense heterozygous pathogenic variants in the *PSEN1* gene linked to autosomal dominant disorder in one patient each (*PSEN1* c.416T>C (case no. 1) and *PSEN1* c.799C>A (case no. 2)) and homozygous nonsense pathogenic variant in the *OPTN* gene linked to autosomal recessive disorders in two more patients (*OPTN* c.403G>T (cases no. 3 and 4)). Furthermore, only one of them is novel (*PSEN1* c.799C>A) and the remaining have already been described in the literature or present in databases. All variants from this group were absent in our control samples. According to ACMG standards and guidelines, all detected potentially disease causing variants were characterized as pathogenic. Further details on described pathogenic variants are provided in Table 1.

All patients carrying the abovementioned variants had a clinical picture in line with the phenotype described for the corresponding gene. The main clinical characteristics of these patients are provided in Table 2 alongside the OMIM number (HAMOSH *et al*., 2005) for their final genetic diagnosis established in this study. Briefly, of the four genetically confirmed patients, two were diagnosed with EOAD and two with FTD.

Relatives of the two probands (cases no. 1 and 2) (Table 2) with *PSEN1* pathogenic variants were not available for the segregation analysis. On the other side, a several asymptomatic relatives of the proband (case no. 3) (Table 2) with *OPTN* homozygous pathogenic variant were examined by direct Sanger sequencing. All tested asymptomatic relatives of this proband carried the variant in a heterozygous state. Further, the symptomatic sister of the other proband (case no. 4) (Table 2) with *OPTN* homozygous pathogenic variant was tested. The analysis revealed that she has the same homozygous *OPTN* variant. Interestingly, she was diagnosed with ALS.

In the remaining 11 cases included in the study, we could not manage to identify a likely genetic cause. Thus, in these cases, genetic diagnosis remains unclear.

Table 1. Variants that represent a likely genetic cause in patients with dementia in Serbia

Gene name	HGVS	Variant type, molecular consequence, and variant location	Clinical significance/ Pathogenicity class*	No. of carriers in 200 Serbian healthy controls	GnomAD v2.1 i 3.1 database MAF	ClinVar accession number #	Theoretical predictions for variants	Inheretance type/zygosity	Citation	Novel variant
PSEN1	*NM_000021.4, c.416T>C, p.M139T*	*SNV, missense, exon*	*Pathogenic-5*	*0*	*Not reported*	*SCV001478336.1*	*MutationTaster: disease causing, CADD: 25.7, MetaLR: damaging, REVEL: pathogenic; Polyphen: probably damaging*	*ad/het*	*ClinVar98023; HGMD:CM951067; LOVD:PSEN1_000247; PMID: 8634712, 11165779, 12433263, 33076948, 10441572, 27466472, 22906081, 22307680, 26481686, 34220489*	*No*
PSEN1	*NM_000021.4, c.799C>A, p.P267T*	*SNV, missense, exon*	*Pathogenic-5*	*0*	*Not reported*	*SCV001450773.1*	*MutationTaster: disease causing, CADD: 25.7, MetaLR: damaging, REVEL: pathogenic; Polyphen: probably damaging*	*ad/het*	*/*	*Yes*
OPTN	*NM_021980.4, c.403G>T, p.E135**	*SNV, nonsense, exon*	*Pathogenic-5*	*0*	*0.0000398*	*SCV001805843.1*	*MutationTaster: disease causing automatic, CADD: 35*	*ar/hom*	*ClinVar631627; PMID: 29650794*	*No*

SNV-single nucleotide variant, ad: autosomal dominant, ar: autosomal recessive; het-heterozygous, hom-homozygous, *classification by ACMG/AMP guidelines (RICHARDS *et al*., 2015); #our submission to ClinVar; CADDv1.6-suggested cutoff on deleteriousness is between 10 and 20

Table 2. Clinical characteristics of patients with dementia included in this study

Case No.	Age, y; Gender	Clinical picture	Final diagnosis	Family history-Goldman score **
1	*49; F*	*Dementia*	*Early onset Alzheimer's disease (OMIM:607822)*	*1*
2	*66;M*	*Dementia, anxiety, vertigo, behavioral changes*	*Early onset Alzheimer's disease (OMIM:607822)*	*1*
3	*56; F*	*Dementia, quadriplegia, aphasia*	*Frontotemporal dementia (OMIM:613435)*	*2*
4	*54; F*	*Dementia, aphasia, dysphagia, depression*	*Frontotemporal dementia (OMIM:613435)*	*3*

y-years; M-male, F-female; ** Goldman score scale- score 1: autosomal dominant if there were at least three people in two generations; score 2: family aggregation if there were at least three relatives with dementia or ALS and criteria for autosomal dominant inheritance were not met; score 3: a single affected first-degree family member with dementia or ALS; score 4: no contributory family history, unknown family history.

DISCUSSION

In our study, we performed the analysis of the CE panel comprising 4813 genes in patients with cognitive disorders. We have investigated 15 unrelated patients diagnosed with various types of early onset dementia. Disease causing genotypes were detected in four unrelated probands. The study analyzed *in silico* created gene subpanels made according to each patient's clinical phenotype using HPO terminology (KÖHLER *et al*., 2021) (https://hpo.jax.org/app), and we observed a diagnostic yield of 26.7%. Previous reports of CE panel analysis in patients with non-selected dementias revealed a diagnostic yield of 33% (ZALAR *et al*., 2018), which is similar to our study.

We detected a rare variant of known significance (p.M139T) in the *PSEN1* gene in one patient with EOAD which has been reported in several European families with EOAD (references provided in Table 1) and is described as disease-causing. One more *PSEN1* variant (p.P267T) has been identified in our analysis in another patient with EOAD that has not been reported in the literature so far. The variant is absent from the worldwide control population (gnomAD) and our cohort of 200 healthy controls. Also, is predicted to be pathogenic by several

in silico prediction tools, and it is in line with the clinical phenotype of our patient. Based on the evidence lines above, we can conclude that p.P267T represents a genetic cause of disease in our patient.

Pathological variants in the *OPTN* gene have been related to FTD (POTTIER *et al*., 2015) and ALS (MARUYAMA *et al*., 2010). *OPTN* detected variant (c.403G>T) in our two unrelated probands has been already described in the literature, but in patients diagnosed with ALS (MÜLLER *et al*., 2018). Thus far, our two probands with FTD are the first cases of FTD without motor neuron disease, caused by homozygous c.403G>T *OPTN* variant. Since evidence of *OPTN* variants related to FTD are scarce, our findings may contribute to the increase of this number. Another significant fact of our study is that a sister of one of our probands with *OPTN* variant (case no. 4) has a clinical diagnosis of ALS. Comorbidity of ALS and FTD is known for many ALS and FTD genes (FREISCHMIDT *et al*., 2015), including *OPTN* (POTTIER *et al*., 2018). However, in our study, we detected for the first time a c.403G>T *OPTN* variant in two sisters having different clinical presentations (one with a clinical diagnosis of FTD and the other with ALS). Hence, our results re-emphasize that ALS and FTD are part of a disease spectrum with an overlapping genetic basis.

We did not identify any likely genetic cause in the remaining 11 patients. The cause of their illness could be a pathological variant in a gene not included in the CE panel or in part of the genome that is not included in the CE panel (such as the deep intronic region, or promoter region). We cannot exclude quantitative or complex structural changes in these cases either. In this regard, expanded panels such as WES and WGS could foster the investigation of additional genetic factors underlying the clinical presentation of patients.

Both AD and FTD are clinically and pathologically heterogeneous disorders characterized by a complex genetic architecture that is not yet completely understood. The heritability rates of the different dementia subtypes range from 40 to 80%, with EOD showing a higher genetic component than late-onset dementia (FERENCZ and GERRITSEN 2015).

The recent development of massively parallel DNA sequencing technologies allows for the systematic screening of individual genomes for DNA sequence variations at base-pair resolution, enabling researchers to uncover novel and/or potentially pathogenic rare variants in candidate genes. As previously documented, targeted re-sequencing of a clinically significant gene panel may represent a cost-time effective technique compared to the previously used sequential Sanger sequencing (BECK *et al*., 2014; PICCOLI *et al*., 2016; XU *et al*., 2018).

In conclusion, we performed CE panel analysis on 15 patients with different cognitive disorders to study the contribution of rare SNVs in selected dementia genes. Our study showed that using the CE panel, which encompasses known genes associated with monogenic dementias, provides a powerful tool for establishing a genetic diagnosis of various types of dementia. Therefore, smaller gene panels could be used as a first step in clinical genetic testing, then, if there is a strong indication for a genetic basis and the mutation was not originally found, expanded gene panel analysis such as WES should be considered. The challenge in interpreting the results obtained by WES/WGS should be taken into account, as well as implementation in clinical practice.

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REFERENCES

ADZHUBEI, I.A., S. SCHMIDT, L. PESHKIN, V.E. RAMENSKY, A. GERASIMOVA, P. BORK, A.S. KONDRASHOV, S.R. SUNYAEV (2010): A method and server for predicting damaging missense mutations. Nat methods, *7* (4), 248–249.

ANDERSON N. D. (2019). State of the science on mild cognitive impairment (MCI). CNS spectrums, *24*(1), 78–87.

APOSTOLOVA L.G. (2016): Alzheimer Disease. Continuum (Minneap Minn), *22* (2 Dementia), 419–434.

BARANDIARAN M., A. ESTANGA, F. MORENO, B. INDAKOETXEA, A. ALZUALDE, N. BALLUERKA, J.F. MARTÍ MASSÓ, A. DE LÓPEZ MUNAIN (2012): Neuropsychological features of asymptomatic c.709–1G > A progranulin mutation carriers. J Int Neuropsychol Soc, *18* (6):1086–1090

BECK, J., A. PITTMAN, G. ADAMSON, T. CAMPBELL, J. KENNY, H. HOULDEN, J.D. ROHRER, R. DE SILVA, M. SHOAI, J. UPHILL, M. POULTER, J. HARDY, C.J. MUMMERY, J.D. WARREN, J.M. SCHOTT, N.C. FOX, M.N. ROSSOR, J. COLLINGE, S. MEAD (2014): Validation of next-generation sequencing technologies in genetic diagnosis of dementia. Neurobiol Aging, *35* (1), 261–265.

BENNION-CALLISTER, J., S.M. PICKERING-BROWN (2014): Pathogenesis/genetics of frontotemporal dementia and how it relates to ALS. Exp Neurol., *262 Pt B,* 84–90.

BERGANT, G., A. MAVER, L. LOVRECIC, G. ČUTURILO, A. HODZIC, & B. PETERLIN (2018): Comprehensive use of extended exome analysis improves diagnostic yield in rare disease: a retrospective survey in 1,059 cases. Genet Med, *20*(3), 303–312.

BONVICINI, C., C. SCASSELLATI, L. BENUSSI, E. DI MARIA, C. MAJ, M. CIANI, S. FOSTINELLI, A. MEGA, M. BOCCHETTA, G. LANZI, E. GIACOPUZZI, S. FERRABOLI, M. PIEVANI, V. FEDI, C.A. DEFANTI, S. GILIANI (2019): Alzheimer's Disease Neuroimaging Initiative, Frisoni GB, Ghidoni R, Gennarelli M. Next Generation Sequencing Analysis in Early Onset Dementia Patients. J Alzheimers Dis., *67* (1):243-256.

BORRONI B., C. BONVICINI, D. GALIMBERTI, L. TREMOLIZZO, A. PAPETTI, S. ARCHETTI, M. TURLA, A. ALBERICI, C. AGOSTI, E. PREMI, I. APPOLLONIO, I. RAINERO, C. FERRARESE, M. GENNARELLI, E. SCARPINI, A. PADOVANI (2011): Founder effect and estimation of the age of the progranulin Thr272fs mutation in 14 Italian pedigrees with frontotemporal lobar degeneration. Neurobiol Aging, *32* (3):555.e1–555.e8

BRANKOVIĆ M., N. DRAGAŠEVIĆ, V. DOBRIČIĆ, A. MAVER, G. BERGANT, I. PETROVIĆ, S. PERIĆ, A. MARJANOVIĆ, M. JANKOVIĆ, J. JANČIĆ, I. NOVAKOVIĆ, B. PETERLIN, M. SVETEL, V. KOSTIĆ (2022): Clinical exome sequencing in Serbian patients with movement disorders - single centre experience. - Genetika, *54* (1): 395-409

CACACE, R., K. SLEEGERS, C. VAN BROECKHOVEN (2016): Molecular genetics of early- onset Alzheimer's disease revisited. Alzheimers Dement., *12* (6), 733–748.

CHAN, K.Y., W. WANG, J.J. WU, L. LIU, E. THEODORATOU, J. CAR, L. MIDDLETON, T.C. RUSS, I.J. DEARY, H. CAMPBELL, W. WANG, I. RUDAN, GLOBAL HEALTH EPIDEMIOLOGY REFERENCE GROUP (GHERG) (2013): Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet, *381* (9882), 2016–2023.

DEPRISTO, M.A., E. BANKS, R. POPLIN, K.V. GARIMELLA, J.R. MAGUIRE, C. HARTL, A.A. PHILIPPAKIS, G. DEL ANGEL, M.A. RIVAS, M. HANNA, A. MCKENNA, T.J. FENNELL, A.M. KERNYTSKY, A.Y. SIVACHENKO, K. CIBULSKIS, S.B. GABRIEL, D. ALTSHULER, M.J. DALY (2011): A framework for variation discovery and genotyping using next-generation DNA sequencing data. Nat. Genet., *43* (5): 491–498.

DOLS-ICARDO, O., A. GARCÍA-REDONDO, R. ROJAS-GARCÍA, D. BORREGO-HERNÁNDEZ, I. ILLÁN-GALA, J.L. MUÑOZ-BLANCO, A. RÁBANO, L. CERVERA-CARLES, A. JUÁREZ-RUFIÁN, N. SPATARO, N. DE LUNA, L. GALÁN, E. CORTES-VICENTE, J. FORTEA, R. BLESA, O. GRAU-RIVERA, A. LLEÓ, J. ESTEBAN-PÉREZ, E. GELPI, J. CLARIMÓN (2018): Analysis of known amyotrophic lateral sclerosis and frontotemporal dementia genes reveals a substantial genetic burden in patients manifesting both diseases not carrying the C9orf72 expansion mutation. J Neurol Neurosurg Psychiatry, *89* (2), 162–168.

FERENCZ, B., L. GERRITSEN (2015): Genetics and underlying pathology of dementia. Neuropsychol Rev., *25* (1), 113–124.

FREISCHMIDT, A., T. WIELAND, B. RICHTER, W. RUF, V. SCHAEFFER, K. MÜLLER, N. MARROQUIN, F. NORDIN, A. HÜBERS, P. WEYDT, S. PINTO, R. PRESS, S. MILLECAMPS, N. MOLKO, E. BERNARD, C. DESNUELLE, M.H. SORIANI, J. DORST, E. GRAF, U. NORDSTRÖM, M.S. FEILER, S. PUTZ, T.M. BOECKERS, T. MEYER, A.S. WINKLER, J. WINKELMAN, M. DE CARVALHO, D.R. THAL, M. OTTO, T. BRÄNNSTRÖM, A.E. VOLK, P. KURSULA, K.M. DANZER, P. LICHTNER, I. DIKIC, T. MEITINGER, A.C. LUDOLPH, T.M. STROM, P.M. ANDERSEN, J. H. WEISHAUPT (2015): Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia. Nat Neurosci., *18* (5), 631–636.

FOKKEMA, I. F., P.E. TASCHNER, G.C. SCHAAFSMA, J. CELLI, J.F. LAROS, J.T. DEN DUNNEN (2011): LOVD v.2.0: the next generation in gene variant databases. Hum. Mutat., *32* (5): 557–563.

GAUTHIER S., P. ROSA-NETO, J.A. MORAIS, C. WEBSTER (2021): World Alzheimer Report 2021: Journey through the diagnosis of dementia. London, England: Alzheimer's Disease International.

GOLDMAN, J. S., J.M. FARMER, E.M. WOOD, J.K. JOHNSON, A. BOXER, J. NEUHAUS, C. LOMEN-HOERTH, K.C. WILHELMSEN, V.M. LEE, M. GROSSMAN, B.L. MILLER (2005): Comparison of family histories in FTLD subtypes and related tauopathies. Neurology, *65* (11), 1817–1819.

GORNO-TEMPINI, M.L., A.E. HILLIS, S. WEINTRAUB, A. KERTESZ, M. MENDEZ, S.F. CAPPA, J.M. OGAR, J.D. ROHRER, S. BLACK, B.F. BOEVE, F. MANES, N.F. DRONKERS, R. VANDENBERGHE, K. RASCOVSKY, K. PATTERSON, B.L. MILLER, D.S. KNOPMAN, J.R. HODGES, M.M. MESULAM, M. GROSSMAN (2011): Classification of primary progressive aphasia and its variants. Neurology, *76* (11), 1006–1014.

GRAFF-RADFORD, N.R., B.K. WOODRUFF (2007): Frontotemporal dementia. Semin Neurol., *27* (1), 48–57.

GREAVES, C. V., J. D. ROHRER (2019): An update on genetic frontotemporal dementia. J Neurol, *266* (8), 2075–2086.

GROSSMAN, M. (2012): The non-fluent/agrammatic variant of primary progressive aphasia. Lancet Neurol., *11* (6), 545–555.

HAMOSH, A.F. SCOTT, J.S. AMBERGER, C.A. BOCCHINI, V.A. MCKUSICK (2005): Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nuc. Acids Res., *33* (Database issue): D514–D517.

HARDY, J., E. ROGAEVA (2014): Motor neuron disease and frontotemporal dementia: sometimes related, sometimes not. Exp Neurol., *262 Pt B*, 75–83.

HINZ, F.I., D.H. GESCHWIND (2017): Molecular Genetics of Neurodegenerative Dementias. Cold Spring Harb Perspec Biol., *9* (4), a023705.

HODGES, J. R., K. PATTERSON, S. OXBURY, E. FUNNELL (1992): Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain, *115* (Pt 6), 1783–1806.

JARMOLOWICZ, A.I., H.Y. CHEN, P.K. PANEGYRES (2015): The patterns of inheritance in early-onset dementia: Alzheimer's disease and frontotemporal dementia. Am J Alzheimers Dis Other Demen., *30* (3), 299–306.

KARCZEWSKI, K.J., L.C. FRANCIOLI, G. TIAO, B.B. CUMMINGS, J. ALFÖLDI, Q. WANG, R.L. COLLINS, K.M. LARICCHIA, A. GANNA, D.P. BIRNBAUM, L.D. GAUTHIER, H. BRAND, M. SOLOMONSON, N.A. WATTS, D. RHODES, M. SINGER-BERK, E.M. ENGLAND, E.G. SEABY, J.A. KOSMICKI, R.K. WALTERS, K. TASHMAN, Y. FARJOUN, E. BANKS, T. POTERBA, A. WANG, C. SEED, N. WHIFFIN, J.X. CHONG, K.E. SAMOCHA, E. PIERCE-HOFFMAN, Z. ZAPPALA, A.H. O'DONNELL-LURIA, E.V. MINIKEL, B. WEISBURD, M. LEK, J.S. WARE, C. VITTAL, I.M. ARMEAN, L. BERGELSON, K. CIBULSKIS, K.M. CONNOLLY, M. COVARRUBIAS, S. DONNELLY, S. FERRIERA, S. GABRIEL, J. GENTRY, N. GUPTA, T. JEANDET, D. KAPLAN, C. LLANWARNE, R. MUNSHI, S. NOVOD, N. PETRILLO, D. ROAZEN, V. RUANO-RUBIO, A. SALTZMAN, M. SCHLEICHER, J. SOTO, K. TIBBETTS, C. TOLONEN, G. WADE, M.E. TALKOWSKI, GENOME AGGREGATION DATABASE CONSORTIUM, B.M. NEALE, M.J. DALY, D.G. MACARTHUR (2020): The mutational constraint spectrum quantified from variation in 141,456 humans. Nature, *581*(7809), 434–443. Epub 2020 May 27. Erratum in: Nature, 2021 Feb; 590(7846):E53.

KÖHLER, S., M. GARGANO, N. MATENTZOGLU, L.C. CARMODY, D. LEWIS-SMITH, N.A. VASILEVSKY, D. DANIS, G. BALAGURA, G. BAYNAM, A.M. BROWER, T.J. CALLAHAN, C.G. CHUTE, J.L. EST, P.D. GALER, S. GANESAN, M. GRIESE, M. HAIMEL, J. PAZMANDI, M. HANAUER, N.L. HARRIS, M.J. HARTNETT, M. HASTREITER, F. HAUCK, Y. HE, T. JESKE, H. KEARNEY, G. KINDLE, C. KLEIN, K. KNOFLACH, R. KRAUSE, D. LAGORCE, J.A. MCMURRY, J.A. MILLER, M.C. MUNOZ-TORRES, R.L. PETERS, C.K. RAPP, A.M. RATH, S.A. RIND, A.Z. ROSENBERG, M. SEGAL, M.G. SEIDEL, D. SMEDLEY, T. TALMY, Y. THOMAS, S. A.WIAFE, J. XIAN, Z. YÜKSEL, I. HELBIG, C.J. MUNGALL, M.A. HAENDEL, P.N. ROBINSON (2021): The Human Phenotype Ontology in 2021. Nuc. Acids Res., *49* (D1): D1207–D1217.

LANDRUM, M.J., J.M. LEE, M. BENSON, G.R. BROWN, C. CHAO, S. CHITIPIRALLA, B. GU, J. HART, D. HOFFMAN, W. JANG, K. KARAPETYAN, K. KATZ, C. LIU, Z. MADDIPATLA, A. MALHEIRO, K. MCDANIEL, M. OVETSKY, G. RILEY, G. ZHOU, J.B. HOLMES, B.L. KATTMAN, D.R. MAGLOTT (2018): ClinVar: improving access to variant interpretations and supporting evidence. Nuc. Acids Res., *46* (D1): D1062–D1067.

LOBO, A., L.J. LAUNER, L. FRATIGLIONI, K. ANDERSEN, A. DI CARLO, M.M. BRETELER, J.R. COPELAND, J.F. DARTIGUES, C. JAGGER, J. MARTINEZ-LAGE, H. SOININEN, A. HOFMAN (2000): Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology, *54* (11 Suppl 5), S4–S9.

MAHONEY C.J, J. BECK, J.D. ROHRER, T. LASHLEY, K. MOK, T. SHAKESPEARE, T. YEATMAN, E.K.WARRINGTON, J.M. SCHOTT, N.C. FOX, M.N. ROSSOR, J. HARDY, J. COLLINGE, T. REVESZ, S. MEAD, J.D. WARREN (2012): Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. Brain, *135* (Pt 3):736–750

MAVER, A., L. LOVRECIC, M. VOLK, G. RUDOLF, K. WRITZL, A. BLATNIK, A. HODZIC, P. BORUT (2016): Phenotype-driven gene target definition in clinical genome-wide sequencing data interpretation. Gen. Med., *18* (11): 1102–1110.

MARUYAMA, H., H. MORINO, H. ITO, Y. IZUMI, H. KATO, Y. WATANABE, Y. KINOSHITA, M. KAMADA, H. NODERA, H. SUZUKI, O. KOMURE, S. MATSUURA, K. KOBATAKE, N. MORIMOTO, K. ABE, N. SUZUKI, M. AOKI, A. KAWATA, T. HIRAI, T. KATO, K. OGASAWARA, A. HIRANO, T. TAKUMI, H. KUSAKA, K. HAGIWARA, R. KAJI, H. KAWAKAMI (2010): Mutations of optineurin in amyotrophic lateral sclerosis. Nature, *465* (7295), 223–226.

MILLER, S.A., D.D. DYKES, H.F. POLESKY (1988): A simple salting out procedure for extracting DNA from human nucleated cells. Nuc. Acids Res., *16* (3): 1215.

MONTAUT, S., C. TRANCHANT, N. DROUOT, G. RUDOLF, C. GUISSART, J. TARABEUX, T. STEMMELEN, A. VELT, C. FOURRAGE, P. NITSCHKE, B. GERARD, J.L. MANDEL, M. KOENIG, J. CHELLY, M. ANHEIM, FRENCH PARKINSON'S AND

MOVEMENT DISORDERS CONSORTIUM (2018): Assessment of a Targeted Gene Panel for Identification of Genes Associated With Movement Disorders. JAMA Neurol., *75* (10): 1234–1245.

MÜLLER, K., D. BRENNER, P. WEYDT, T. MEYER, T. GREHL, S. PETRI, J. GROSSKREUTZ, J. SCHUSTER, A.E. VOLK, G. BORCK, C. KUBISCH, T. KLOPSTOCK, D. ZELLER, S. JABLONKA, M. SENDTNER, S. KLEBE, A. KNEHR, K. GÜNTHER, J. WEIS, K.G. CLAEYS, B. SCHRANK, A.D. SPERFELD, A. HÜBERS, M. OTTO, J. DORST, T. MEITINGER, T.M. STROM, P.M. ANDERSEN, A.C. LUDOLPH, J.H. WEISHAUPT; GERMAN ALS NETWORK MND-NET (2018): Comprehensive analysis of the mutation spectrum in 301 German ALS families. J Neurol Neurosurg Psychiatry, *89* (8), 817–827.

OGAR, J.M., N.F. DRONKERS, S.M. BRAMBATI, B.L. MILLER, M.L. GORNO-TEMPINI (2007): Progressive nonfluent aphasia and its characteristic motor speech deficits. Alzheimer Dis Assoc Disord., *21* (4), S23–S30.

OKAZAKI, T., M. MURATA, M. KAI, K. ADACHI, N. NAKAGAWA, N. KASAGI, W. MATSUMURA, Y. MAEGAKI, E. NANBA (2016): Clinical Diagnosis of Mendelian Disorders Using a Comprehensive Gene-Targeted Panel Test for Next-Generation Sequencing. Yonago Acta Med., *59* (2): 118–125.

PAJUSALU, S., T. KAHRE, H. ROOMERE, Ü. MURUMETS, L. ROHT, K. SIMENSON, T. REIMAND, K. ÕUNAP (2018): Large gene panel sequencing in clinical diagnostics-results from 501 consecutive cases. Clin. Genet., *93* (1): 78–83.

PICCOLI, E., G. ROSSI, T. ROSSI, G. PELLICCIONI, I. D'AMATO, F. TAGLIAVINI, G. DI FEDE (2016): Novel PSEN1 mutations (H214N and R220P) associated with familial Alzheimer's disease identified by targeted exome sequencing. Neurobiol Aging, *40*, 192.e7–192.e11.

POTTIER, C., K.F. BIENIEK, N. FINCH, M. VAN DE VORST, M. BAKER, R. PERKERSEN, P. BROWN, T. RAVENSCROFT, M. VAN BLITTERSWIJK, AM. NICHOLSON, M. DETURE, DS. KNOPMAN, KA. JOSEPHS, JE. PARISI, RC. PETERSEN, KB. BOYLAN, BF. BOEVE, NR. GRAFF-RADFORD, JA. VELTMAN, C. GILISSEN, ME. MURRAY, DW. DICKSON, R. RADEMAKERS (2015): Whole-genome sequencing reveals important role for TBK1 and OPTN mutations in frontotemporal lobar degeneration without motor neuron disease. Acta Neuropathol., *130* (1):77-92.

POTTIER, C., E. RAMPERSAUD, M. BAKER, G. WU, J. WUU, J.L. MCCAULEY, S. ZUCHNER, R. SCHULE, C. BERMUDEZ, S. HUSSAIN, A. COOLEY, M. WALLACE, J. ZHANG, J.P. TAYLOR, M. BENATAR, R. RADEMAKERS (2018): Identification of compound heterozygous variants in OPTN in an ALS-FTD patient from the CReATe consortium: a case report. Amyotroph Lateral Scler Frontotemporal Degener., *19* (5-6), 469–471.

PRINCE, M., R. BRYCE, E. ALBANESE, A. WIMO, W. RIBEIRO, C.P. FERRI (2013): The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement., *9* (1), 63–75.e2.

RASCOVSKY, K., J.R. HODGES, C.M. KIPPS, J.K. JOHNSON, W.W. SEELEY, M.F. MENDEZ, D. KNOPMAN, A. KERTESZ, M. MESULAM, D.P. SALMON, D. GALASKO, T.W. CHOW, C. DECARLI, A. HILLIS, K. JOSEPHS, J.H. KRAMER, S. WEINTRAUB, M. GROSSMAN, M.L. GORNO-TEMPINI, B.M. MILLER (2007): Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): current limitations and future directions. Alzheimer Dis Assoc Disord., *21* (4), S14–S18.

RASCOVSKY, K., J.R. HODGES, D. KNOPMAN, M.F. MENDEZ, J.H. KRAMER, J. NEUHAUS, J.C. VAN SWIETEN, H. SEELAAR, E.G. DOPPER, C.U. ONYIKE, A.E. HILLIS, K.A. JOSEPHS, B.F. BOEVE, A. KERTESZ, W.W. SEELEY, K.P. RANKIN, J.K. JOHNSON, M.L. GORNO-TEMPINI, H. ROSEN, C.E. PRIOLEAU-LATHAM, A. LEE C.M. KIPPS, P. LILLO, O. PIGUET, J.D. ROHRER, M.N. ROSSOR, J.D. WARREN, N.C. FOX, D. GALASKO, D.P. SALMON, S.E. BLACK, M. MESULAM, S. WEINTRAUB, B.C. DICKERSON, J. DIEHL-SCHMID, F. PASQUIER, V. DERAMECOURT, F. LEBERT, Y. PIJNENBURG, T.W. CHOW, F. MANES, J. GRAFMAN, S.F. CAPPA, M. FREEDMAN, M. GROSSMAN, B.L. MILLER (2011): Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain, *134* (Pt 9), 2456–2477.

REALE, C., C. PANTEGHINI, M. CARECCHIO, B. GARAVAGLIA (2018): The relevance of gene panels in movement disorders diagnosis: A lab perspective. Eur. J Paediatr Neurol., *22* (2), 285–291.

RENTZSCH, P., M. SCHUBACH, J. SHENDURE, M. KIRCHER (2021): CADD-Splice-improving genome-wide variant effect prediction using deep learning-derived splice scores. Genome Med., *13* (1): 31.

RICHARDS S., N. AZIZ, S. BALE, D. BICK, S. DAS, J. GASTIER-FOSTER, W.W. GRODY, M. HEGDE, E. LYON, E. SPECTOR, K. VOELKERDING, H.L. REHM, ACMG LABORATORY QUALITY ASSURANCE COMMITTEE (2015): Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet. Med., *17* (5): 405–424.

SACHS-ERICSSON, N., D. G. BLAZER (2015): The new DSM-5 diagnosis of mild neurocognitive disorder and its relation to research in mild cognitive impairment. Aging & mental health, *19*(1), 2–12.

SAUNDERS, A.M., W.J. STRITTMATTER, D. SCHMECHEL, P.H. GEORGE-HYSLOP, M.A. PERICAK-VANCE, S.H. JOO, B.L. ROSI, J.F. GUSELLA, D.R. CRAPPER-MACLACHLAN, M.J. ALBERTS (1993): Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology, *43***,** 1467-72.

SCHWARZ, J.M., C. RÖDELSPERGER, M. SCHUELKE, D. SEELOW (2010): MutationTaster evaluates disease-causing potential of sequence alterations. Nat. Methods, *7* (8): 575–576.

SEELAAR, H., J.D. ROHRER, Y.A. PIJNENBURG, N.C. FOX, J.C. VAN SWIETEN (2011): Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. J Neurol Neurosurg Psychiatry, *82* (5), 476–486.

SIEBEN, A., T. VAN LANGENHOVE, S. ENGELBORGHS, J.J. MARTIN, P. BOON, P. CRAS, P.P. DE DEYN, P. SANTENS, C. VAN BROECKHOVEN, M.CRUTS (2012): The genetics and neuropathology of frontotemporal lobar degeneration. Acta Neuropathol., *124* (3), 353–372.

SMITS, L.L., A.C. VAN HARTEN, Y.A. PIJNENBURG, E.L. KOEDAM, F.H. BOUWMAN, N. SISTERMANS, I.E. REULING, N.D. PRINS, A.W. LEMSTRA, P. SCHELTENS, W.M. VAN DER FLIER (2015): Trajectories of cognitive decline in different types of dementia. Psychol Med., *45* (5), 1051–1059.

SNOWDEN J.S., S. ROLLINSON, J.C. THOMPSON, J.M. HARRIS, C.L. STOPFORD, A.M. RICHARDSON, M. JONES, A. GERHARD, Y.S. DAVIDSON, A. ROBINSON, L. GIBBONS, Q. HU, D. DUPLESSIS, D. NEARY, D.M. MANN, S.M. PICKERINGBROWN (2012): Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72mutations. Brain *135* (Pt 3):693–708

STENSON, P.D., E.V. BALL, M. MORT, A.D. PHILLIPS, J.A. SHIEL, N.S. THOMAS, S. ABEYSINGHE, M. KRAWCZAK, D.N. COOPER (2003): Human Gene Mutation Database (HGMD): 2003 update. Hum. Mutat., *21* (6): 577–581.

XU, Y., X. LIU, J. SHEN, W. TIAN, R. FANG, B. LI, J. MA, L. CAO, S. CHEN, G. LI, H. TANG (2018): The Whole Exome Sequencing Clarifies the Genotype- Phenotype Correlations in Patients with Early-Onset Dementia. Aging Dis., *9* (4), 696–705.

ZALAR, B., A. MAVER, A. KOVANDA, A. PETERLIN, B. PETERLIN (2018): Clinical exome sequencing in dementias: a preliminary study. Psychiatr Danub, *30* (2):216-219.

ANALIZA PANELA "KLINIČKI EGZOM" KOD BOLESNIKA SA KOGNITIVNIM POREMEĆAJIMA U POPULACIJI SRBIJE

Marija BRANKOVIĆ [1, 2], Elka STEFANOVA[1,2], Gorana MANDIĆ[1,2], Ana MARJANOVIĆ[1,2], Valerija DOBRIČIĆ[3], Aleš MAVER[4], Gaber BERGANT[4], Zorica STEVIĆ[1,2], Milena JANKOVIĆ[1], Ivana NOVAKOVIĆ[2], Borut PETERLIN[4], Vladimir KOSTIĆ [1,2]

[1]Klinika za neurologiju, Univerzitetski Klinički Centar Srbije, Beograd, Srbija
[2]Medicinski fakultet, Univerzitet u Beogradu, Beograd, Srbija
[3]Luebeck Interdisciplinarna platforma za analizu genoma (LIGA), Univerzitet u Libeku, Nemačka
[4]Klinički Institut za Medicinsku Gentiku, Univerzitetski Medicinski Centar Ljubljana, Ljubljana, Slovenija

Izvod

Kako se starosna granica pomera, demencija postaje sve veći problem javnog zdravlja. Prema trenutnim procenama, skoro 50 miliona ljudi u svetu boluje od demencije, a očekuje se da će broj obolelih rasti. U našoj studiji analizirali smo genetičku osnovu kognitivnih poremećaja sekvenciranjem kliničkog egzoma. Studija je obuhvatila ukupno 15 nesrodnih bolesnika sa dijagnozom različitih kognitivnih poremećaja, koji su bili negativni nakon ciljanih genetičkih testiranja dostupnih na Neurološkoj klinici, UKCS, Beograd, Srbija. Prilikom selekcije bolesnika, prednost su imali porodični slučajevi sa ranom prezentacijom bolesti ili složenim fenotipom. Sekvenciranje panela kliničkog egzoma koji obuhvata 4813 gena povezanih sa poznatim kliničkim fenotipima izvedeno je na Illumina MiSeq NGS platformi prema uputstvima proizvođača. Rezulati sekvenciranja su analizirani pomoću Variant Studio v3 softvera kao i internog pipelina. Analiza i interpretacija varijanti zasnovane su na analizi virtualnih genskih panela odabranih prema fenotipu pacijenta, pretraživanju literature i baza podataka, učestalosti alela i in silico analizama. Uzročne varijante su potvrđene Sangerovim sekvenciranjem. Kod pojedinih članova porodice rađene su segregacione analize. Utvrđen je verovatni genetički uzrok kognitivnih poremećaja kod četiri bolesnika. Analizom panela klinički egzom detektovane su dve misense heterozigotne patogene varijante u genu PSEN1 kod dva nesrodna bolesnika i jedna nonsens homozigotna patogena varijanta u genu OPTN kod još dva nesrodna bolesnika. Detektovane patogene varijante su u skladu sa kliničkim fenotipom datih bolesnika. Kod preostalih 11 slučajeva, genetička dijagnoza je za sada nerazjašnjena. Rezultati naše studije naglašavaju značaj analize panela kliničkog egzoma u rasvetljavanju dijagnoze kognitivnihporemećaja i daju nam uvid u složenost genetičke pozadine ove grupe poremećaja.

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