REVIEW

of Prof. DRAGA TONCHEVA, MD, Corresponding member of BAS, DSc, MU Sofia, appointed at a meeting of the scientific jury on 23.12.2020 as a reviewer in a competition for the academic position of "Associate Professor" position of "Associate Professor" at Sofia University "St. Kliment Ohridski ", in the professional field 7.1. Medicine, specialty "Medical Genetics", published in the State newspaper no. 88/ 13.10.2020

Common part

The competition for Associate Professor of Medicine, specialty in medical genetics, has been announced for the needs of Sofia University "St. Kliment Ohridski ". The only candidate in the competition for associate professor, code 7.1 is Dr. Radoslava Vasileva Vazharova, Ph.D. The review of the documents showed that the procedure for opening and announcing the competition was followed. The materials for the competition are prepared in accordance with the requirements of the Law for the development of the academic staff in the Republic of Bulgaria and the Regulations for its application at Sofia University "St. Kliment Ohridski".

Dr. Radoslava Vasileva Vazharova

CV

Radoslava Vasileva Vazharova was born in 1969 in the city of Sofia.

In 1976 she graduated with excellent results from secondary education at ESPU with teaching in German (diploma A88 №066546, reg. №3429 / 03.07.1988), and in 1994 - higher education Master of Medicine at Higher Medical Institute Sofia with excellent results (Diploma № 012341, reg. № 41201 / 27.12.1994).

Dr. Vazharova has a scientific specialty in "Medical Genetics" (Certificate Series AC № 006691, reg. №004828 / 10.02.2000).

She has obtained the educational and scientific degree "Doctor" in the field of Genetics with a dissertation "Analytical approach to the detection of genetic disorders in rare diseases through DNA sequencing of a new generation" (Diploma Series MIA №000486, reg. № 429-D / 20.07. 2016).

Dr. Vazharova has worked as an assistant and chief assistant successively in: the Department of Medical Genetics, Faculty of Medicine, MU - Sofia as (1995 - 2008); in the Department of Obstetrics and Gynecology of the Ministry of Finance, MU-Sofia (2008-2012) and in the Department of Biology, Medical Genetics and Microbiology, Medical Faculty of Sofia University "St. Kliment Ohridski "(from 2012 until now).

Dr. Vazharova is a recognased teacher with extensive experience. She has trained students of medicine, pharmacy and specialists in the Department of Medical Genetics at the Medical Faculty, Medical University of Sofia, she has delivered a module "Genetic diseases, antenatal screening and prenatal diagnosis of genetic diseases and congenital anomalies" at the Department of Obstetrics and Gynecology and is a lecturer in medical genetics to medical students at the Department of Biology, Medical Genetics and Microbiology, Faculty of Medicine, Sofia "St. Kliment Ohridski ".

Specializations and professional skills:

She has completed specialized courses at international institutes: FISH analysis at the Department of Genetic Ecotoxicology, The Institute of Experimental Medicine, Prague, Czech Republic (December 2007); ArrayCGH analysis in BlueGnome, Cambridge, UK (November 2008); in the genetic laboratory of the Gustave Roussy Institute, Paris, France (November 2009) and in OGT, Oxford, Begbroke, UK (May 2010).

She has experience in a wide range of laboratory diagnostic methods: cell culture, cytogenetic analysis (prenatal, postnatal), molecular cytogenetic analysis (FISH, arrayCGH, SNParray) and for the first time in Bulgaria introduces massive parallel sequencing at MiSeq Illumina platform, as well as analysis and interpretation of data from different types of genetic research. She works with specialized software products - CytoVision® (Leica Biosystems), CytoSure Interpret (OGT), BlueFuse Multi (BlueGnome, Illumina), VariantStudio (Illumina), VarAft, Galaxy and others.

She was a medical-genetic consultant at the National Genetic Laboratory, SBALAG "Mother's Home" of patients and their families with genetic diseases, predispositions and congenital anomalies. She performs analyzes of large databases obtained by microarray study of copy number variants and data from NGS sequencing in the genetic laboratory of SBALGAR "Dr. Malinov"; performs diagnostic activities in the Laboratory of Medical Genetics and Molecular Biology of Hospital "Lozenets" EAD.

She is a member of the Bulgarian Medical Union, Bulgarian Society of Human Genetics and Genomics, Bulgarian Alliance for Precision and Personalized Medicine, European Society of Human Genetics

Scientific projects

In the last 5 years Dr. Vazharova has been a member of research teams of projects:

- DN03 / 7 (18.12.2016) funded by Nacional Scientific Fund (NSF), Ministry of Education and Science (MES), under the Competition for financing basic research (2016), on the topic “Characterization of longevity genes through genomic and target sequencing”, finished;

- KP-06-N33 / 5 of 13.12.2019, funded by the NSF, MES, under the Competition for funding of basic research - 2019, on the topic “Comparative characteristics of genome/exome and antibody repertoire in Bulgarian patients with Alzheimer's, frontotemporal and unspecified dementia”, current;

- KP-06PN-43/31, funded in the last session of the NSF, MES on the topic "Innate immune response to RNA-viral pathogens. Evaluation of the role of variants in RLRs / TLRs genes in the host signaling pathways using a SARS-CoC-2 invasion model”, supervisor Dr. R. Vazharova;

- She is a participant in an international project that won a grand in the last session of the NSF "Competition for projects under bilateral cooperation programs - international competition for joint research projects for KOVID-19", supervisor Assoc. Prof. V. Terzieva.

Scientific works

Overview of scientific publications

Dr. Vazharova has the necessary scientific production for "Associate Professor".

She is the author and co-author of 54 scientific publications, of which:

- 6 publications in connection with the dissertation;
- 48 publications outside the dissertation
- publications outside the dissertation

Publications outside the dissertation

- 10 publications in peer-review journals, indexed in Scopus, Web of Science (Habilitation thesis - B4), IF - 12,044;
- 12 publications in international journals with IF - 25,987;
- 26 publications in non-refereed scientific journals without IF (5 publications in international journals and 21 in national scientific journals).

The total Impact Factor is 38,031. Dr. Vazharova's scientific publications have been cited 208 times.

She is co-author of chapters from 2 books and 2 textbooks.

Dr. Vazharova has 34 participations in International scientific forums. Outside of the dissertation she has 29 participations with plenary and section reports at the Balkan Congress of Human Genetics in Plovdiv (2017), Edirne, Turkey (2019) and Thessaloniki, Greece (2004); poster participation in the 53rd ESHG Conference June 6-9, 2020 (Virtual Conference); 52nd ESHG Conference June 15-18, 2019, Gothenburg, Sweden; 51st ESHG Conference June 16-19, 2018, Milan, Italy; 50th ESHG Conference May 27-30, 2017, Copenhagen, Denmark and 5 participations in national scientific forums.

In terms of the total number of indicators, she significantly exceeds the minimum set for the academic position of "Associate Professor" (3508.71 score as compared to the minimum of 400).

The publications on the dissertation have already been reviewed and that is why I accept 48 scientific papers for review.

Evaluation of the scientific contributions in the habilitation work

Ten articles published in peer-reviewed journals (with a total impact factor of 11,719) are presented as habilitation work (indicator B4). The results are published in: Biotechnology and Biotechnological Equipment 2018; 32 (6): 1345-1351; Biotechnology and Biotechnological Equipment 2018; 32 (3): 679-685; Sexual Development 2017; 11 (1): 21-28; Balkan Journal of Medical Genetics 2008; 11 (1): 33-40; Clin Genet 2014; 85: 452-457; Balkan J Med Genet 2018; 21 (2): 59-62; Balkan Journal of Medical Genetics 2002; 5 (1 & 2): 41-46; Prenat Diagn 10 March 2004; 24 (3): 202-208; Comptes rendus de l'Academie bulgare des Sciences 2018; 71 (11): 1557-1565; Acta Medica Bulgarica 2010; 37 (2): 80-84.

The articles include results, analyzes and new data on the genetic diagnosis and clinical heterogeneity of severe rare diseases due to monogenic defects. A mutation in the *SCN8A* gene with a neurodegenerative effect has been demonstrated.

- Based on the specific phenotypic characteristics, Dr. Vazharova suggested that the mutation in *SCN8A* gene - NM_014191.3: c.5616G> A, NP_055006.1: p.Arg1872Gln has a neurodegenerative effect independent of the epileptogenic one in a patient with infantile epileptic encephalopathy-13. New gene variants associated with a complex cardiovascular phenotype have been discovered and new evidence has been presented that the severity of the clinic is influenced by the mutational load determined by a "digene" rather than a "monogenic" defect. Frequencies of rare and polymorphic alleles in the SRD5A2 gene in the

Bulgarian population were determined. A rare case of double heterozygote by R141H / V231M mutations associated with complex metabolic disease and structural CNS defect has been demonstrated. These results are obtained by applying advanced technologies such as massive parallel sequencing.

Interesting and new for science results have been obtained by using microarray to determine complete genomic disorders. The etiology, molecular pathogenesis and phenotype-genotype correlations in rare chromosomal diseases have been determined. Microdeletion defects have been identified in congenital malformations that are problematic for diagnosis and interpretation. Heterozygous microdeletion 9q21.11-q21.2 and extremely rare chromosomal rearrangement - familial complex translocation comprising chromosomes 1, 4, 9, 20 have been proven. A novelty for science is a structural chromosomal defect that is associated with a phenotype of monogenic disease (APC promoter 1 deletion).

These results have scientific value, as the diagnosis of rare diseases has become possible through new technologies for genomic analysis. The obtained data also have important practical significance for the development of precision medicine.

The research of Dr. Vazharova is related to another very important scientific aspect - the introduction of methods for determining fetal aneuploidies by DNA fragment analysis of polymorphic STR markers. She contributes to the implementation of National program for prevention of hereditary diseases, predispositions and congenital anomalies and the functioning of the National Program for Rare Diseases.

Rare diseases are debilitating and severe disorders. They are the most difficult subject for genetic analysis because they have a very low population frequencies. Therefore, the results obtained for each individual case with innovative technologies is a contribution to the science. The identification of molecular defects in the genome associated with human diseases opens up new perspectives for medical practice and for the development of precision medicine - accurate diagnosis and development of new targeted therapies.

Evaluation of the scientific contributions of publications outside the habilitation work

Scientific achievements:

The data obtained by Dr. Vazharova in these publications are impressive and convincingly prove the role of innovative technologies to achieve high results in a new scientific field - genomic medicine.

The publications submitted for review, outside the habilitation work, cover the following topics:

• Genetic determination of rare monogenic and chromosomal diseases and congenital malformations;

• Phenotype-genotype correlations in complex diseases - schizophrenia, bipolar disorder, Balkan endemic nephropathy;

• Genetic factors for longevity.

- New variants associated with monogenic or complex diseases have been identified: two mutations in the *CYP11B1, CPT2, ACTA2* genes (publ. 16, 23, 28). Data from the screening for inversion 22 (Inv22) in the coagulation factor VIII gene in Bulgarian patients with severe hemophilia were obtained (publ. 48).

- 14 extremely rare gene variants (pathogenic, possibly pathogenic, VUS) associated with clinical phenotypes have been identified. They are deposited in the ClinVar database (document named ClinVar - Submission Portal - NCBI.pdf, at 15.Artefact.rar).

- 3 candidate genes for susceptibility to Balkan endemic nephropathy have been nominated (publ. 12).

- Strong candidate genes for predisposition to psychiatric diseases - bipolar disorder and schizophrenia have been identified in large-scale genomic studies of SNPs variants in Bulgarian cases / controls (publ. 13, 14, 20, 21, 25);

- Exome analyzes of Bulgarian centenarians provide evidence for new variants in longevity genes (publ. 26, 27). Centenarian's exome has been used as a benchmark for prioritizing genetic variants of clinical significance associated with a tumor suppressor effect or predisposing to cardiovascular disease (Publications 18 and 19).

Scientific and applied achievements

- In the pediatric clinical practice, advanced methods for genomic analysis of patients with monogenic diseases, chromosomal/microdeletion/microduplication syndromes, malformative syndromes and intellectual deficiency have been introduced and popularized - SNParray, arrayCGH, massive parallel 30 sequencing of 34.).

Significant results have been achieved in the diagnosis of lysosomal storage diseases (publ. 31).

The prognostic value of PAPP-A between 11 and 13 + 6 g.s. to assess the risk of developing preeclampsia (publ. 33).

The possibilities of ultrasound screening for Down syndrome and other chromosomal abnormalities have been refined by measuring fetal nuchal translucency (publ. 42).

EDUCATIONAL ACTIVITY

Dr. Vazharova is a specialist in medical genetics, with over 25 years of experience as a teacher of medical and pharmaceutical students and doctors specializing in medical genetics as an assistant and chief assistant at the Department of Medical Genetics at the Ministry of Finance, MU-Sofia and students. of Medicine at the Department of Biology, Medical Genetics and Microbiology, Medical Faculty of Sofia University "St. Kliment Ohridski ". She has trained students and graduates in the Department of Obstetrics and Gynecology at MU - Sofia.

She has broad knowledges and extensive erudition in medical genetics and is highly appreciated by colleagues, students and patients. She has given lectures to students. Dr. Vazharova was an invited speaker in the plenary session of the 12th Balkan Congress of Human Genetics, on September 8-10, 2017, Plovdiv, Bulgaria "Application of targeted NGS in diagnostic work-up of patients with rare diseases" and has presented two section reports on "WES analysis on rare diseases" at the 13th Balkan Congress of Human Genetics, Edirne, Turkey, 17 -20 April 2019, and "Prenatal cytogenetic diagnosis - frequency and type of detected chromosomal aberrations", 6th Balkan Meeting on Human Genetics, Thessaloniki, Greece 2004.

Dr. Vazharova is a co-author of two books: "Clinical management in ovarian cancer", 2014, Editor D. Kalev. Publ. house Art Tracer, ISBN 978-619-7094-11-4, pp. 25-42 and of "Rare Genetic Diseases", 2014, Editor D. Toncheva, Publ. house Simelpress, ISBN 978-619-184-012-1, pp. 18-31; 238-265; 266-304.

She is a co-author in two textbooks: "Tests in Medical Genetics", Editor D. Toncheva, Knowledge Ltd. 2004, ISBN: 954-621-212-1, p. 173; "Medical genetics in clinical practice - a guide for doctors and students", 1999, Editor D. Toncheva, ed. Ciela, ISBN: 95464491993, pp. 106-114.

MEMBERSHIP IN SCIENTIFIC ORGANIZATIONS:

Dr. Vazharova is a member of the following scientific and professional organizations:

• Bulgarian Medical Association;

• Bulgarian Society of Human Genetics and Genomics;

• Bulgarian Alliance for Precise and Personalized Medicine;

• European Society of Human Genetics

CONCLUSION

Dr. Vazharova is a prominante creative person, with established authority among geneticists in Bulgaria, respected by patients as a doctor-consultant in medical genetics and a charming teacher. She meets all the criteria for holding the academic position of "Associate Professor": she has a doctoral dissertation, serious publications in international journals with a high overall impact factor. Dr. Vazharova has significant scientific achievements, original scientific and applied research results in the field of rare diseases, screening programs for genetic diseases and problems of medical and genetic counseling. He has a recognized specialty in medical genetics since 2000.

Dr. Vazharova introduces in research and clinical practice new advanced technologies for comprehensive genomic analysis of genetic disorders. The results achieved by it contribute to the elucidation of the molecular pathogenesis underlying the studied diseases and are relevant to the molecular diagnosis, prognosis and therapeutic behavior of patients.

Dr. Vazharova is an university lecturer with a leading position in the field of medical genetics at Sofia University “St. Kliment Ohridski ”.

With all this in mind, I would like to strongly recommend Dr. Radoslava Vazharova to the esteemed Scientific Jury to award the title of Associate Professor of Medicine, for the needs of Sofia University "St. Kliment Ohridski ”

29.01.2021

Reviewer:

Corr. member of BAS, prof. Draga Toncheva

Department of medical genetics, Medical University - Sofia