Review

in a competition for the academic position of associate professor,
professional field 7.1. Medicine (Medical Genetics),
for the needs of the Medical Faculty, announced in SG, issue 88/13.10.2020

Reviewer: Prof. Dr. Varban Stoyanov Ganev, PhD, DSci, Sofia University "St. Kliment Ohridski "

1. General provisions and biographical data

On the basis of order № RD 38-601/16.12.2020 and on the grounds of Art. 4 and Art. 25 of the Law for the Development of the Academic Staff in the Republic of Bulgaria (ZRASRB), Art. 57 Para. (1) and Para. (2) of the Regulations for application of the Law for the Development of the Academic Staff in the Republic of Bulgaria, Art. 108 Para. (1) and Para. (3) of the Regulations for the Conditions and the Order for Acquiring Scientific Degrees and Holding Academic Positions in Sofia University "St. Kliment Ohridski ", decision of the Faculty Council of the Medical Faculty (Minutes № 83 of 10.12.2020) with Decision of the Scientific Jury on this competition (Minutes №1, 29 December 2020) I have been appointed as a reviewer on a competition for acquisition of academic position associate professor by professional field 7.1. Medicine (Medical Genetics), for the needs of the Medical Faculty, announced in SG, issue 88/13.10.2020. Based on the submitted materials for participation in the competition, one candidate was admitted to it - Dr. Radoslava Vasileva Vazharova, Doctor, who at the time of application was chief assistant professor in the Department of Biology, Medical Genetics and Microbiology, Faculty of Medicine, Sofia University "St. Kliment Ohridski ".

Dr. Radoslava Vazharova was born on September 8, 1969 in the city of Sofia. She graduated from high school with German language teaching with excellent results. In 1994 she graduated from the Higher Medical Institute - Sofia, with honors, and obtained a Master's Degree in medicine. She has held academic positions from assistant to chief assistant professor in medical genetics at the Department of Medical Genetics at the Medical Faculty, Medical University - Sofia (1995-2008), at the Department of Obstetrics and Gynecology at the Medical Faculty, Medical University Sofia (2008-2012) and in the Department of Biology, Medical Genetics and Microbiology, Faculty of Medicine, Sofia University "St. Kliment Ohridski "(since 2012). She defended her doctoral dissertation in the field of competition on "Analytical Approach to the Detection of Genetic Disorders in Rare Diseases Through DNA Sequencing of a New Generation" (2016).

She has a recognized specialty in medical genetics since 2000. She has participated in specialized courses in FISH analysis - December 2007, Department of Genetic Ecotoxicology, The Institute of Experimental Medicine, Prague, Czech Republic, and ArrayCGH analysis - November 2008, BlueGnome, Cambridge, UK and November 2009 - Genetics Laboratory of the Gustave Roussy Institute, Paris, France; May 2010, OGT, Oxford, Begbroke, UK. These trainings on the most modern technologies with application in genetic research for

scientific and diagnostic purposes have undoubtedly contributed a lot to the progress in the technological readiness of Dr. Radoslava Vazharova. Currently, she is competent in addition to routinely applied methods of diagnosis and research and the latest approaches: cell culture, cytogenetic analysis (prenatal, postnatal), molecular cytogenetic analysis (FISH, arrayCGH, SNParray), molecular genetic methods (massive parallel sequencing on MiSeq Illumina), analysis and interpretation of data from various types of genetic research, incl. work with specialized software products - CytoVision® (Leica Biosystems), CytoSure Interpret (OGT), BlueFuse Multi (BlueGnome, Illumina), VariantStudio (Illumina), VarAft, Galaxy and others.

Along with the academic positions, Dr. Radoslava Vazharova was a specialist in medical genetics, SBALAG "Mother's Home" EAD, genetic consultant at the National Genetic Laboratory (2008-2012), a specialist in medical genetics in the genetic laboratory of SBALGAR "Dr. Malinov" (2012-2017), a specialist in medical genetics in the Laboratory of Medical Genetics and Molecular Biology of MHAT "Lozenets" EAD (since 2017). She is a member of the Bulgarian Medical Union, the Bulgarian Society of Human Genetics and Genomics, the Bulgarian Alliance for Precise and Personalized Medicine and the European Society of Human Genetics.

2. The compliance with the minimum national requirements and with the additional requirements of Sofia University "St. Kliment Ohridski"

According to the provisions of Art. 109 Para. (3), Art. 105 Para. (1) Item 4, Art. 107 Para. (1) Item 12 of the Regulations on the Terms and Conditions for Acquiring Scientific Degrees and Holding Academic Positions at Sofia University "St. Kliment Ohridski ", the members of the scientific jury must take a stand on the compliance of the candidates' achievements with the minimum national requirements and with the additional requirements of Sofia University" St. Kliment Ohridski ". Dr. Radoslava Vazharova has attached in her documents on the competition her reference on the criteria for the minimum national requirements under Art. 2b of ZRASRB. From the reference and the attached evidence regarding the data, it can be seen that the performance indicators of the applicant significantly exceed the minimum national requirements (MNR). In particular:

Group of indicators A - 50 points (MNR - 50 points)

Group of indicators B - not required for the academic position of associate professor

Group of indicators B - 121.38 points (MNR - 100 points)

Group of indicators D - 278.71 points (MNR - 200 points)

Group of indicators D - 3110 points (MNR - 50 points)

Group of indicators E - 100 points (not required for the academic position of associate professor)

It can be categorically said that Dr. Radoslava Vasileva Vazharova, Doctor, definitely exceeds the minimum national requirements for the academic position of associate professor.

3. Evaluation of the indicators related to the educational activity

Throughout her academic career over 25 years, Dr. Radoslava Vasileva Vazharova, Doctor, has taught medical genetics. The reference presented by the Medical Faculty of Sofia University "St. Kliment Ohridski" shows that during the last three full academic years (2016/2017, 2017/2018 and 2018/2019) Dr. Radoslava Vazharova has taught medical genetics through practical exercises of medical students in Bulgarian and English and has a classroom employment of 1620 teaching hours (900 teaching hours in Bulgarian and 720 teaching hours in English). In addition, she participated as a member of the examination commission in the exams in medical genetics of students and for the same period tested 288 students. Apart from teaching medical students, she has also participated in the teaching of medical genetics to pharmacy students, as well as as an instructor in practical training of specialized doctors (medical genetics and obstetrics and gynecology).
The teaching work of Dr. Radoslava Vazharova is characterized by excellent preparation of training materials, and I especially want to point out that a large part of these materials are from Dr. Vazharova's own practice in medical-genetic consultation and laboratory diagnostics. Conducting some of the practical activities of Dr. Vazharova in the natural working environment of medical genetics specialists contributes to an understanding of the completeness and depth of the genetic research.

In conclusion, I can confidently say that Dr. Radoslava Vasileva Vazharova, PhD is an erudite lecturer in medical genetics, with excellent professional training and well-deserved authority and trust of the students and graduates.

4. Evaluation of indicators related to research

The research activity of Dr. Radoslava Vasileva Vazharova, Doctor, respectively of the scientific field in which it develops - medical genetics, is multifaceted and includes clinical genetics (rare genetic diseases - phenotypic heterogeneity, mechanisms of occurrence, diagnosis), modern methods for genetic diagnostics in monogenic diseases, chromosomal/microdeletion/microduplication syndromes, malformative syndromes and intellectual deficit (microchip analysis, massive parallel sequencing), genetic predisposition to common diseases, genetic factors for longevity.

Dr. Radoslava Vasileva Vazharova participated in the competition with a dissertation for the award of educational and scientific degree "Doctor" on "Analytical Approach to the Detection of Genetic Disorders in Rare Diseases Through DNA Sequencing of a New Generation" and 48 articles (22 in journals, which are referenced and indexed in international databases, 26 in non-referenced journals with scientific review). In addition, Dr. Vazharova has 29 participations in international and 4 participations in national scientific forums.

Ten of the articles mentioned above are presented as habilitation work. They carry a total impact factor: 11.72. Four of these articles have been cited 41 times, with 19 of the citations being in the last 5 years.

Apart from the articles from the habilitation work, there are 12 papers in journals with impact factor, five are in international journals with scientific review, 21 are in national medical journals with scientific review, 29 are participations in international scientific forums and 4 are participations in national scientific forums. The total impact factor of the publications from this group is 26.00. They have been cited a total of 157 times.

A significant part of the works presented for publication have found a worthy evaluation by leading journals in the field of medical genetics such as the Journal of Human Genetics, Clinical Genetics, Journal of Inherited Metabolic Disease, Prenatal Diagnosis, or specialized journals such as Sexual Development, Genes, Brain and Behavior, Journal of Affective Disorders, Psychiatric Genetics, Gynecological Endocrinology, Technology in Cancer Research & Treatment, as well as scientific publications from the country and the region such as Balkan Journal of Medical Genetics, Biotechnology and Biotechnological Equipment, Comptes rendus de l'Acad´emie Bulgare des Sciences and Acta Medica Bulgarica.

The dissertation of Dr. Radoslava Vazharova is dedicated to the study of the etiology of rare genetic diseases through massive parallel sequencing (New Generation Sequencing, NGS). The main challenge in using this toolkit is the interpretation of the data obtained with it and their use in the context of a specific clinical application. This is the first for our country systematic application of NGS, the results of which are summarized in a dissertation. The work on this work, together with the work on a number of cases, formed in the above-mentioned publications in specialized publications and scientific events, as well as the daily diagnostic activity with application of NGS by Dr. Radoslava Vazharova and assign the authority of a leading specialist in our country in this area.

The main contributions of Dr. Radoslava Vazharova in the group of 10 articles from the group of habilitation work can be summarized as follows:

(1) The first three articles and the last article are devoted to patients with rare monogenic diseases - infantile epileptic encephalopathy type 13, hypertrophic cardiomyopathy, 5-alpha reductase deficiency and PMM2-CDG. The contribution to these works is in the significant shortening of the path from the appearance of the first symptoms to the molecular diagnosis (genetic defect) thanks to three of the four cases of the application of massive parallel sequencing. The first article describes the first patient in this country with a mutation in the SCN8A gene, in whom a genetic defect SCN8A NM_014191.3:c.5616G > A, NP_055006.1:p.Arg1872Gln was detected, supposed neurodegenerative defect independent of epileptogenic defect. The second article describes new gene variants in patients with a complex cardiovascular phenotype. The third article of the sample describes the first Bulgarian patients with 5-alpha reductase deficiency, determined frequencies of rare and polymorphic alleles in the SRD5A2 gene in the Bulgarian population, using data from massive parallel sequencing. The last article in this group described a rare case of combining metabolic disease with a structural CNS defect and discussed on possible links between the two conditions.

(2) Another group of four articles is devoted to chromosomal diseases, where the contribution is in the clarification of the etiology of the disease and the establishment of phenotype-genotype correlations.

The first three articles in this sample describe rare forms of genetic defects that are problematic for diagnosis and clinical interpretation: mosaic forms of chromosomal and microstructural deletions; microdeletion of a gene promoter. A case is described in which a structural chromosomal defect appears phenotypically as a monogenic disease due to an effect on gene expression - (deletion APC promoter 1B). The fourth article in this series describes extremely rare chromosomal rearrangements and discusses the challenges associated with similar findings in prenatal diagnosis.

(3) Two other articles are devoted to the care of the mother and her unborn child during pregnancy within the National Program for Prevention of Hereditary Diseases, Predispositions and Congenital Anomalies and the National Program for Rare Diseases. The articles present approaches for the detection of fetal aneuploidies by DNA fragment analysis of polymorphic STR markers, as well as by the use of biochemical parameters in the blood of the pregnant woman. Both articles share efforts to adapt approaches to prenatal screening and diagnosis of chromosomal aneuploidies to the conditions of our healthcare and to apply them in the best way in clinical practice.

The main contributions of Dr. Radoslava Vazharova in the published works outside the above in the group of habilitation work are in two directions: clinical and genetic characterization of rare monogenic/chromosomal diseases and polymalformative syndromes and disclosure of phenotype-genotype associations in complex phenotypes , cardiovascular diseases, neuromuscular diseases, longevity. There are several contributions:

(1) New genetic variants associated with monogenic diseases have been discovered.

(2) Fourteen extremely rare gene variants of phenotypic significance (pathogenic, probably pathogenic, VUS) have been deposited in the ClinVar database - document ClinVar - Submission Portal - NCBI.pdf.

(3) Application in practice and popularization of advanced methods for genetic analysis - SNParray, arrayCGH, massive parallel sequencing of exome.

Results from the research work of Dr. Radoslava Vazharova are presented at scientific events in Bulgaria and abroad. Her plenary report at the 12th Balkan Congress of Human Genetics, held on September 8-10, 2017, Plovdiv, Bulgaria, was awarded. Topic: "Application of targeted NGS in diagnostic work-up of patients with rare diseases".

Scientific publications authored and co-authored by Dr. Radoslava Vazharova are cited in 208 scientific publications, 207 of which are in referenced and indexed publications in international databases and one is in a non-referenced scientific publication.

Dr. Radoslava Vazharova has participated in research projects as a member of the research team in two projects funded by the NSF, MES:

1) DN03 / 7 (18.12.2016) Competition for funding basic research (2016), topic: "Characterization of Longevity Genes through Genomic and Target Sequencing", Head: Corresponding Member Prof. Draga Toncheva, DSci, MD, finished.

(2) KP-06-N33 / 5 (13.12.2019), Competition for funding of basic research - 2019, topic: "Comparative Characteristics of Genomic/Exomic Spectra and Antibody Repertoire in Bulgarian Patients with Alzheimer's, Frontotemporal and Unspecified Dementia ", supervisor: Corresponding Member Prof. Draga Toncheva, DSci, MD, current.

In addition, Dr. Radoslava Vazharova is the leader of a project ranked for funding in the last session of the NSF for basic research, № KP-06-PN-43/31, topic: "Innate Immune Response to RNA-Viral Pathogens. Evaluation of the Role of Variants in RLRs/TLRs Genes of Host Signaling Pathways Using a Model of SARS-CoV-2 Invasion."

Dr. Radoslava Vazharova is a co-author and participant in an international project that won a grant in the last session of the NSF Competition for projects under bilateral cooperation programs - international competition for joint research projects for KOVID-19, topic: "Functional Role of Follicular Helper and Regulatory T Cells for the Production and Maintenance of SARS-CoV-2 Neutralizing Antibody Levels".

In conclusion, Dr. Radoslava Vasileva Vazharova, Doctor, is a well-established researcher in the field of medical genetics, competently mastering a wide arsenal of modern technologies for research and diagnostic work, with the ability to work in multidisciplinary teams and the potential to lead her own modern research. I am fully convinced that it will contribute significantly to the smooth and increasingly convincing presentation of the scientific potential of the team with which she works.

5. Personal impressions and opinion

My personal impressions of Dr. Radoslava Vasileva Vazharova date back more than 20 years, and in the last eight years they are quite immediate due to her joining our team. I have witnessed the research and teaching activities of Dr. Radoslava Vazharova. My impressions are that in her face the academic community finds a very prepared and responsible scientist and teacher who is able to involve in the creative process not only colleagues but also students. This gives me reason to believe that its pursuit of continuous development will push it to continue to seek more and more opportunities for assimilation and application in research and diagnostic work of constantly evolving new technological and information platforms.

I can say without any hesitation that Dr. Radoslava Vasileva Vazharova, Doctor, meets all the requirements for the academic position of Associate Professor, and her achievements in teaching and research in the field of medical genetics far exceed generally accepted standards.

6. Conclusion

In the announced competition for acquiring the academic position of Associate Professor in a professional field 7.1. Medicine (Medical Genetics), for the needs of the Medical Faculty, announced in SG, issue 88/13.10.2020, one candidate participated - Dr. Radoslava Vasileva Vazharova, Doctor, who at the time of application was Chief Assistant Professor in the Department of Biology, Medical Genetics and Microbiology, Faculty of Medicine, Sofia University "St. Kliment Ohridski ".

Based on the materials provided for the professional activity of Dr. Radoslava Vasileva Vazharova, as well as my personal impressions, I confidently declare that I give a positive assessment to the candidate for the academic position of associate professor in the professional field 7.1. Medicine (Medical Genetics), for the needs of the Faculty of Medicine, Sofia University "St. Kliment Ohridski ". I recommend that the members of the scientific jury join this assessment and also vote in favor.

Sofia, February 11, 2021.

Signature: