EDITORIAL

Future has come: next-generation sequencing in the diagnostics of orphan diseases

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Orphan diseases are a great problem for clinicians due to their low frequency in different populations and geographic regions [1, 2]. Approximately 6,172 unique rare diseases (RDs) are known to exist and new ones are discovered each year, 71.9% of which are genetic and 69.9% of which are exclusively pediatric onset cases. RDs affect between 262.9 and 446.2 million people worldwide and approximately 17.8–30.3 million people in the European Union [3]. Therefore, RDs have become a global public health priority (NGO Committee for Rare Diseases. Statements of support to the NGO Committee for Rare Diseases. 2016. https://www.ngocommitteeerarediseases.org/statements-of-support/). Another important issue is the high cost of the RD diagnostic procedures for the health-care system, which frequently cover the evaluation costs of not only the patient, but also the patient's family members, and hence, this should also be taken into consideration in the planning of the diagnostic procedure.

The manifestation of orphan diseases is not always fully symptomatic, making the clinical diagnosis of specific orphan diseases difficult. Moreover, the complexity of the genetic background of RDs is challenging [4, 5, 6]. The typical example of a genetic germline aberration associated with a different clinical phenotype is the von Hippel Lindau disease (VHL) (Online Mendelian Inheritance in Man [OMIM] 193300). VHL is an autosomal dominantly inherited syndrome (1/36,000 live births), predisposing carriers to the development of highly vascularized malignant and benign tumors [7]. The largest groups of causative mutations of the VHL gene include missense mutations (50%) and deletions of one or more exons (30%). Other described defects consist of nonsense mutations, splicing site mutations, micro-insertions, or micro-deletions [5, 6]. The VHL gene plays a key role in the oxygen-sensing pathway in targeting the subunits of the hypoxia-inducible factor (HIF; a sequence-specific DNA-binding transcription factor) for proteasomal degradation [8]. Abnormal interaction of mutated VHL-HIF is responsible for the activation of transcription of >200 target genes involved in angiogenesis, metabolism, apoptosis, and oxygen homeostasis, which determine the different phenotypes of the VHL disease [9]. Homozygous germline mutations of the VHL gene have been responsible for a specific form of secondary congenital erythrocytosis – Chuvash polycythemia (OMIM 2634000; erythrocytosis type 2, autosomal recessive).

In 2020, the first Polish family carrying a variant of the VHL gene (c.598C>T) associated with Chuvash polycythemia was identified. The presence of mutation was confirmed with the help of the 203 gene panel next-generation sequencing (NGS) technique in two siblings (homozygotes) and in both parents (heterozygotes). The genetic diagnostics of Chuvash polycythemia is challenging, especially in infants and young children; therefore, diagnostic success is important [10]. It is mainly due to the fact that many other genetic variants belonging to different metabolic pathways (oxygen sensing, erythropoiesis, and oxygen transport) have been identified as the cause of erythrocytosis [11]. The recently proposed inherited erythrocytosis-targeted NGS panel includes only 21 genes from the relevant pathways [12]. The above-mentioned strategy allows reduction in the high cost of the NGS procedure. The number of genes studied, however, should be chosen cautiously. The usage of a large gene panel and the NGS technique allowed to identify other disease-associated genes and, with the help of segregation analysis (reverse phenotyping), made it possible to associate new symptoms with a well-known disease phenotype [13]. On the other hand, it should be always kept in mind that the qualification for genetic diagnostics should proceed with a drastic selection of patients with erythrocytosis on the basis of an evaluation of the erythropoietin blood concentration and the oxygen tension at which hemoglobin is 50% saturated (P_{50}) value to exclude hemoglobin variants with high oxygen affinity [14].

In conclusion, the application of advanced genetic techniques, including NGS studies, is the future of orphan disease diagnostics. The presented data concerning the Polish family with Chuvash polycythemia is an excellent example of this.

Authors' contributions

KL – the only author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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