Chapter

Introductory Chapter: Rare Diseases - Ending the Diagnostic Odyssey and Beginning the Therapeutic Odyssey

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1. Introduction

Rare disease is any disease or condition that affects a small percentage of the population. For instance, in the United States, a rare disease is defined as a condition that affects fewer than 200 000 people, whereas in Europe, a disease is considered rare when it affects less than 1 in 2000 people within the general population. Thus, a rare disease is a health condition that affects small number of people compared with other prevalent diseases in the general population [1]. However, specific issues are raised with respect to their rarity. This implies that a disease can be rare in one region, but common in another region, for example, thalassemias, a heterogeneous group of genetic disorders of blood that reduces the production of functional hemoglobin (the protein in red blood cells that carries oxygen). Thalassemia is rare in Northern Europe but more common in the Mediterranean region as well in South and South-East Asia.

Since rare diseases are numerous, heterogeneous in nature, and geographically disparate, rare diseases are an emerging global public health priority. Until now, between 6000 to 8000 distinct rare diseases have been discovered, and new rare diseases are reported constantly in the medical literature [1]. In general, rare diseases affect more than 25 million people in the United States alone, 30 million people in the European Union, and more than 400 million people Worldwide. Generally, 72% of rare diseases are genetic origin and almost 70% of rare diseases are exclusively of pediatric onset, according to the Orphanet, a publicly available epidemiological database that contains information on 6172 unique rare diseases [2].

When of genetic origin, rare disease can be inherited, with several other affected family members, following different modes of inheritance; or they may arise in sporadic, with no other affected family members; or may occur due to *de novo* chance mutations in candidate genes. For several rare conditions, on the one hand, the signs of disease could be observed prior to or during delivery or in childhood, as in the case of achondroplasia, osteogenesis imperfecta (OI, brittle bone disease), spinal muscular atrophy (SMA), or Rett syndrome (RTT). On the other hand, the initial presentation of rare diseases can be observed only during adulthood, as in the case of Huntington's disease (HD, Huntington's Chorea), amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), Crohn's disease (IBD, inflammatory bowel disease), or Charcot–Marie–Tooth Disease (CMT, hereditary motor and sensory neuropathies). While in essence all genetic diseases are rare diseases, not all rare diseases are of genetic diseases. This indicates that there are

also rare forms of non-genetic rare diseases including certain types of autoimmune diseases and rare cancers, such as systemic lupus erythematosus (SLE) and Kaposi sarcoma (KS), respectively. As well as maladies caused by infectious or toxic agents.

2. Evolving challenges and next frontiers

Rare diseases are often complex, may involve chronic illness, disability, and often premature death. As well they are characterized by a remarkably diverse set of symptoms; and relatively common symptoms can mask the underlying rare diseases, leading to frequent misdiagnosis. Symptoms can vary not only from one rare disease to another rare disease but also from one patient to another patient suffering from the same rare disease; even occasionally, the symptoms can differ from a family member to a relative with the same genetic change. At present, a few hundred rare diseases have any available treatments, in most cases, neither a cure nor highly effective treatment is available.

Due to their rarity, patients suffering from rare disease often face certain common problems and challenges, such as delay in getting a correct diagnosis; lack of information and/or scientific knowledge on their own disease; lack of appropriate healthcare; as well as difficulties and inequities in accessing treatment and care. The other lingering obstacles in developing treatment, such as safe and effective drugs and biological products for rare diseases, are due to difficulties in diagnosis; small numbers and geographically dispersed patients and scientific experts; a lack of data from natural history studies; missing biomarkers to support the clinical development of new therapeutics; as well a perception of high economic risk in developing drugs that would serve either a relatively small population with a rare disease or a larger population suffering from a common disease that primarily affects developing countries.

Understandably, nearly all rare disease patients, including their families, have endured the consequence of the so-called diagnostic odyssey, i.e., a period that encompasses from the initial disease recognition or symptom onset to the date of a definitive diagnosis, involving a battery of tests and multiple clinical visits and/or referrals, sometimes for several years, all with the hope of identifying the etiology of their disease. For more than twenty-five percent of rare disease patients, on an average it takes five years before they could be assigned a definite genetic diagnosis. Besides, some people will remain undiagnosed for their entire life.

The methodology of genetic testing of rare diseases depends critically on the exactness of the following three questions, considering β-thalassemia as an example: (1) whether the patient harbors the *specific disease causing variant* in the *specific gene*, for instance, in the case of β-thalassemia, 80% of all mutations in Greek Cypriots are c.93-21G>A; or (2) whether the patient harbors *any variant* in the β-thalassemia gene; or (3) whether the patient harbors *any variant* in *any gene* that would be responsible for his or her medical condition. Each of the above three questions can be addressed by employing methods that can detect: (1) specific sequence changes in the candidate gene; or (2) sequencing each exon of the candidate gene, probably by Sanger sequencing; or (3) by using next generation sequencing (massively parallel sequencing) technology, respectively.

With the advent of next generation sequencing platforms, such as the massively parallel/deep sequencing, has opened up the possibility of rapid identification of the disease-causing genes and genes alterations that are responsible for numerous rare diseases previously characterized only by clinical description [3]. This new technology can be harnessed in several ways for clinical molecular diagnostics purposes with its own advantages and disadvantages, for instance, one can sequence a panel of candidate genes or whole exome using exome capture kits or whole

genome. The major advantage of the whole genome diagnostic sequencing compared with whole exome diagnostic sequencing is that it avoids exon capture, and this would allow changes outside coding exons to be identified routinely.

However, over the last decade, research and clinical exome sequencing efforts have been successfully harnessed at identifying not only known but missed diagnoses but also novel and newly characterized rare genetic syndromes [4, 5]. The utility of clinical exome sequencing resulted, with a diagnostic yield in the range of twenty-five to thirty percent among large and heterogeneous rare diseases cohorts [6]. Nevertheless, in more than seventy percent of patients in whom there was high degree of pre-test probability for a monogenic rare disease, exome sequencing renders no molecular diagnosis.

Despite the remarkable capability of exome sequencing to provide molecular diagnoses for rare disease patients, some pathogenic genomic variants are entirely missed by exome sequencing, for example, small insertions-deletions (indels), chromosomal rearrangements, and copy-number variants (CNVs), but these causative variants can be conclusively diagnosed by short-read genome sequencing. Similarly, rare disease secondary to pathogenic repeat expansions or rearrangements can potentially be identified or enhanced by long-read genomic sequencing. In addition, some disease mechanisms are either difficult or impossible to detect using whole exome sequencing approach, for instance, mosaicism of a pathogenic variant may not be routinely discovered by existing analytical approaches, which requires deep sequencing of multiple tissues. Even though whole genome sequencing outperforms exome sequencing, several other emerging technologies, such as transcriptome sequencing (to evaluate the functional consequence of variants) and methylation arrays (to provide insights into imprinting disorders), offer added value as adjunct diagnostic tools [7].

In general, several clinical investigations have the potential to reveal findings that are not related to the primary reason for the investigation, but that may be clinically significant. Evidently, when a patient's whole exome or whole genome sequencing is performed, it has exceptionally high potential to discover clinically relevant incidental findings. Arguably, the additional concern surrounding the whole exome and/or whole genome sequencing is how to handle the incidental findings, as they become ever more routine. In this context, the European Society of Human Genetics recommends a much more conservative approach, i.e., whenever possible, testing should be targeted to genome regions linked to the patient's indications [8–10].

Finally, the advancement of genetic medicine and precision medicine can end one odyssey and start another one, i.e., for rare disease patients, a genetic result can mark not only the end of a '*diagnostic odyssey*' but also mark the beginning of a '*therapeutic odyssey*.'

3. Conclusions

Rare diseases, even though individually rare, are collective common. Many rare conditions are not only chronically debilitating and progressive but also degenerative and life-threatening. Most do not have appropriate treatments, rendering them incurable. Consequently, drug, biologic, and device development in the case of rare disease is challenging for many reasons, including the complex biology and the lack of critical understanding of the nature course of many rare diseases. In addition, the inherently fewer population of patients with a rare disease may also cause conducting clinical trials challenging. Scientists and clinicians around the globe are working to find better ways to prevent, detect, and treat rare diseases, and to improve the quality of life of patients and their families.

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