Editorial

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Intractable and rare diseases research

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Intractable diseases, literally derived from the Japanese word 'nanbyo', mainly refer to rare diseases that have resulted mostly from unidentifiable causes and/or lack of clearly established or curable treatments. Currently, it is estimated that there are 5,000-7,000 distinct rare diseases worldwide, of which 80% have been identified as having genetic origins and 50% occuring in childhood and lasting for a lifetime (*1,2*). It is worth noting that most cancers including all cancers affecting children are within the scope of the concept of rare disease (*2*). Rare diseases bring patients substantial physical suffering and psychological despair due to the lack of therapeutic hope and the absence of practical support for everyday life. In addition, these kinds of diseases require a significant amount of labor for the patient's care, causing a heavy burden on other family members, both financially and mentally. Although each specific disease affects a limited number of patients because of its rarity, the total number of patients with rare diseases represents a striking proportion of the total population. For example, in the European Union (EU) countries approximately 30 million people, which accounts for 6-8% of the total EU population, have various rare diseases (*2*). In the United States (US), it is estimated that 10% of the people suffer from rare diseases (*3*). These facts indicate that the situation of preventing and controlling rare diseases is grim in the world.

Owing to the relentless work of patient and parent organizations, the previously neglected status of these so called 'orphan diseases' has attracted the attention of public health authorities and policy makers in recent decades. With the incentives of the Orphan Drug Act enacted in the US in 1983 and subsequently similar legislation in Japan, Australia and EU, the number of approved orphan drugs has substantially increased. Thus far, approximately 360 and 60 orphan drugs, in which drugs for rare cancers account for 30-40%, are available for rare disease patients in the US and EU (*4,5*). Nevertheless, it is estimated that only ~10% of rare diseases have an available treatment (also including food supplements, devices and nutraceuticals in addition to drugs), and such treatments can often still be improved (*4*). Even for those diseases that have certain therapeutic strategies, many patients still encounter challenges in receiving appropriate care due to low disease awareness and delayed diagnosis. In the long run, strengthening basic and applied research on rare diseases would benefit patients from better diagnosis and more treatment choices.

Early and accurate diagnosis of a rare disease is of critical importance for those particular patients. Take infantile Pompe's disease as an example, the start of treatment after 6 months of age is considered to be too late for those patients. However, the current situation of identification of a specific rare disease is not optimistic. Statistical data demonstrate that the time from appearance of the clinical symptoms to correct diagnosis is within a range of 5-30 years on average (*4*). That is largely because of the lack of scientific knowledge of the pathology of rare diseases for physicians. Moreover, a rare disease is sometimes masked by a host of other conditions, which may lead to misdiagnosis or highly risky delays for accurate diagnosis. Consequently, poor or late diagnosis may lead to multiple medical consultations, inaccurate treatments, inappropriate behavior and inadequate support from family members, and even for other children born with the same disease in the same family. In this regard, increased knowledge of the disease mechanisms and natural courses will potentially allow better diagnosis of rare diseases. In addition, constructing diagnostics and treatment center networks, training physicians in relevant fields, and appropriate screening for rare diseases in a large population especially in children would help identify patients with rare diseases in an early and comprehensive manner.

Despite the growing public awareness of rare diseases in the last several decades, there are still many gaps in knowledge in developing therapeutic tools and defining therapeutic strategy. Biomedical research on rare diseases will provide insights into the pathologies of diseases and illustrate their underlying mechanisms, which may ultimately reveal possible avenues to therapeutics. Once biomedical research identifies suitable drug candidates and becomes more translational, it will be keenly focused by the industry

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with the aim to provide safe and effective orphan drugs. It is interestingly noted that there is a positive relationship between the number of published papers on a particular rare disease and the likelihood of initiation of an orphan drug development program for that disease. Specifically, there have been 154 rare diseases on each of which more than 600 published papers exist that have one or more drug designations, respectively, between 1983 and 2007 in the US and between 2000 and 2007 in the EU. On the other hand, the number of rare diseases with 200-600 published papers and drug designations were only 42 in that same time period (*6*). These figures demonstrated the significance of biomedical research on rare diseases.

The more a rare disease is known, the more likely it is diagnosed rapidly and covered by effective medical intervention. The acquisition and diffusion of scientific knowledge is the vital basis for identification of diseases, and most importantly, for research into new diagnostic and therapeutic procedures. *Intractable & Rare Diseases Research* is being launched in the context of the serious conditions of rare diseases as well as the few such professional journals worldwide covering this topic. It is founded to promote information exchange among researchers active in the field of rare diseases and various difficult and complicated diseases research in the world, and to cultivate and develop a global medical and drug information network. Finally, patients and families together with health professionals including doctors, scientists and healthcare providers are co-producing a knowledge base, which will improve the quality of life of those patients with intractable and rare diseases.

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