# Attention Should be Drawn to Rare Diseases and Interpretation of Sequence Variants

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The last Monday in February is the "Rare Disease Day" every year. This year the theme of it is "Join us in making the voice of rare diseases heard", proposed by World Health Organization (http://www.rarediseaseday.org). Rare diseases are a group of serious chronic diseases, with a high morbidity and mortality rates. Most of the rare diseases (about 80%) are caused by genetic variants.[1] A specific rare disease generally has a low prevalence, which is about 0.10–0.75% in the United States and the European Union definition; however, with a great variety of rare diseases (about 6000–8000 reported in http://www.orpha.net), the total number of the patients is considerable. In China, a country with the largest population in the world, rare diseases are not uncommon, and the number of the patients affected by rare diseases is great. Therefore, we should pay much more attention to rare diseases, and more focuses on basic and clinical researches on these diseases are needed in China.

There are a large proportion of rare diseases involving in the nervous system. In this issue, attention was drawn to rare neurological diseases, including Charcot-Marie-Tooth disease (CMT), paroxysmal kinesigenic dyskinesia (PKD), autoimmune encephalitis, cubital tunnel syndrome, and dermatomyositis. Genetic factors contribute a lot to CMT and PKD, which cause a great need to the application of sequencing to the molecular diagnosis of these diseases. Recently, next generation sequencing (NGS) was used much more in the clinical practice,[2,3] however, much greater caution should be needed while using it. In the guidelines for investigating the causality of sequence variants in human disease published by MacArthur *et al*.,[4] the authors suggested to pay attention to the whole aspects of using NGS, including selection of technological and analytical approaches, sequencing data quality-control assessments, variations identification, human sequence databases using in silico analysis and replication studies, ethics issues, etc. In 2015, a more detailed and standard interpretation of sequence variants was introduced by American College of Medical Genetics and Genomics (ACMG).[5] In this issue, Sun *et al*.[6] used NGS to explore 79 unrelated patients with a clinical diagnosis of CMT and found three novel rare variants in *GJB1* gene (c.643C>T, c.191G>A and c.610C>T) in three families. As they did not offer the NGS quality-control data, the co-segregating analysis, etc., it was not being suggested to definitely define these three novel rare variants to be the disease pathogenic mutations immediately. More detailed analysis and rigorous criterion to interpret the sequence variants suggested by ACMG should be adopted. In another paper, Wang *et al*.[7] tried to explore the genetic factors in *PRRT2*-negative PKD patients with candidate gene strategy. All the patients were excluded *PRRT2* mutations and the authors conducted genetic testing for *MR-1* and *SLC2A1* genes mutations in the patients, which are the causative genes of paroxysmal nonkinesigenic dyskinesia (PNKD) and paroxysmal exertion-induced dyskinesia (PED), respectively. PNKD and PED have similar syndromes with PKD, which could have same potential pathogenesis with PKD. In the paper, Wang *et al*.[7] found the patients with a clinical diagnosis

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of PKD carrying a novel rare genetic variant of *SLC2A1*. Furthermore, as the definition of pathogenic variants is strict according to ACMG, the conclusion that the new identified rare genetic variants are the disease pathogenic mutations should be with cautions. After the exclusion of the potential clinical misdiagnosis of PED with PKD, and as the *SLC2A1* mutations have a dominated inheritance, if the identified rare novel heterozygous c.363G>A could be verified to be a *de novo* variant or more replications are available in larger sample or in functional assay, it will be a more confident evidence to determine the pathogenesis of c.363G>A.

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