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COMMENTARY

A commentary on *ANKRD11* variants cause variable clinical features associated with KBG syndrome and Coffin–Siris-like syndrome

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Recent advances in genomic analyses based on next-generation sequencing (NGS), as represented by whole-exome sequencing (WES), have yielded very powerful tools to analyze the genetic causes of Mendelian diseases in humans. NGS has enabled the identification of the causative genes in many genetic diseases, which occur as sporadic or small family cases.[1,2]

The identification of causative genes or pathogenic variants among patients suspected to have genetic diseases has led to clarify the relationship between genetic diseases and the same signaling pathways or protein complexes. For example, the concept that the disease of the same category such as RASopathy is newly established.[3,4] In addition, NGS-based analyses have identified pathogenic variants among patients with atypical symptoms. Besides, these analyses have revealed some patients with digenic or trigenic diseases or with pathogenic variants in double genes.[5,6]

Further, NGS analysis can resolve the cases that were clinically difficult to clarify using differential diagnosis due to the overlap between the symptoms of each patient. Therefore, the phenotypic spectrums of some diseases are beginning to be clarified.

Miyatake *et al.*[7] revealed phenotypic diversity in KBG syndrome using WES analysis in patients. They reported three novel variants and one reported variant of the *ANKRD11* gene among five patients displaying varied phenotypic features. In two patients, the phenotypic features overlapped between KBG syndrome and Coffin–Siris syndrome. In fact, the two patients were initially diagnosed with Coffin–Siris-like syndrome. NGS-based analysis could genetically diagnose KBG syndrome in those patients. The analysis could also make diagnose one patient with extremely mild phenotype as KBG syndrome. The WES diagnosis showed that phenotypes of KBG syndrome had a wide spectrum. Reconfirmation of phenotypic features among these patients showed that all patients fulfilled the proposed diagnostic criteria for KBG syndrome.[5]

NGS-based analyses, such as WES or WGS, are quite effective for the molecular diagnosis of genetic diseases. Therefore, a 'genomic first' approach is spreading in multiple fields of medicine, particularly clinical genetics; some scientists and clinicians might think that a diagnosis can be made using the data from NGS alone.

Although the 'genomic first' approach is one among the useful approaches to diagnose patients, it should be noted that there is a risk of misdiagnosis if genomic data are used alone at this moment. Because, since multiple variants have been identified to be pathogenic using WES data in each individual, it is difficult to decide which variant is causative in patients without including additional information such as phenotypic features.

In Miyatake's paper, the final diagnosis for all patients was performed using a combination of clinical and genomic data. Clinical and physical examinations are still very important to diagnose as well as understand diseases. Therefore, both forms of data must be carefully obtained for each patient when analyzing genotype–phenotype correlations or when trying to understand the spectrum of a genetic disease.

As the paper suggests, investigations into the phenotypic diversity of genetic diseases in patients after assured genomic diagnosis will be important to determine disease aspects and these studies will go on increasing.

Currently, whole-exome or whole-genome data are principally used to find only a genotype–phenotype correlation in one causative gene or to find the spectrum of a genetic disease in humans. By contrast, genetic analyses in other species, such as mice, have revealed many modifier genes for monogenic disorders.[8] By studying the spectrum of genetic diseases and analyzing the whole-genome data, modifier genes will be able to be identified in many monogenic diseases in humans as well.

In future, the accumulation and integration of whol-genome data (variants data) and clinical findings in genetic disease patients will allow us to better understand not only the diseases themselves but also the genomic background affecting phenotypes (including a number of modifier genes) in many diseases.

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1 Stranneheim, H. & Wedell, A. Exome and genome sequencing: a revolution for the discovery and diagnosis of monogenic disorders. *J. Intern. Med.* **279**, 3–15 (2016).
2 Rabbani, B., Mahdieh, N., Hosomichi, K., Nakaoka, H. & Inoue, I. Next-generation sequencing: impact of exome sequencing in characterizing Mendelian disorders. *J. Hum. Genet.* **57**, 621–632 (2012).
3 Aoki, Y., Niihori, T., Inoue, S. & Matsubara, Y. Recent advances in RASopathies. *J. Hum. Genet.* **61**, 33–39 (2016).
4 Pevex, U., Rozman, N., Gorsek, B. & Kunej, T. RASopathies: presentation at the genome, interactome,

and phenome levels. *Mol. Syndromol.* **7**, 72–79 (2016).
5 Lupski, J. R. Digenic inheritance and Mendelian disease. *Nat. Genet.* **44**, 1291–1292 (2012).
6 Khateb, S., Zelinger, L., Mizrahi-Meissonnier, L., Ayuso, C., Koenekoop, R. K., Laxer, U. *et al.* A homozygous nonsense CEP250 mutation combined with a heterozygous nonsense C2orf71 mutation is associated with atypical Usher syndrome. *J. Med. Genet.* **51**, 460–469 (2014).
7 Miyatake, S., Okamoto, N., Stark, Z., Nabetani, M., Tsurusaki, Y., Nakashima, M. *et al. ANKRD11* variants cause variable clinical features associated with KBG syndrome and Coffin–Siris-like syndrome. *J. Hum. Genet.* **62**, 741–746 (2017).
8 Vo, A. H. & McNally, E. M. Modifier genes and their effect on Duchenne muscular dystrophy. *Curr. Opin. Neurol.* **28**, 528–534 (2015).