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COMMENTARY

A commentary on exome sequencing identifies a *de novo* mutation in HDAC8 associated with Cornelia de Lange syndrome

Liangdan Sun

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The paper recruited a trio including a patient affected with Cornelia de Lange syndrome (CdLS).[1] It is a multisystem disease resulting from the target gene mutation in accordance with the Mendelian principle. Major clinical manifestations include fused eyebrows (synophrys), long eyelashes, thin lips, small hands and feet, proximally set thumbs and fifth finger clinodactyly.

The syndrome probably affects other organs as well, but the phenotypes are not always the same. Micrognathia, hearing loss and low anterior hairline can be absent in the clinical features.[2] To date, five genes have been found to be the underlying cause of CdLS, which affect the construction and function of cohesion.

The authors adopted a *de novo* strategy based on exome sequencing to explore the causative gene of CdLS. Previous disease-searching methods always need large families and ignore small families or sporadic cases. However, the genetic diseases with severe phenotype, especially the syndromic diseases, were mainly distributed in sporadic forms. In the clinical observation, large familial aggregation of these diseases is rare. It is difficult to reveal inherited bases in these patients until *de novo* strategy applied in exome sequencing. *De novo* mutations in these patients can be identified by using a family-based exome sequencing approach. By sequencing the exome of the patients as well as their parents, *de novo* candidates can be selected by filtering out all inherited variants.[3] This will yield a limited number of potential pathogenic variants, as the average exome contains only 0–3 *de novo* mutations.[4] Vissers *et al.*[5] had revealed the genetic burdens resulting from the *de novo* point mutations in 7 out of 10 patients with intellectual disability, this viewpoint can also be replicated in finding the 35 affected individuals with CdLS proposed by Kaiser *et al.*[6] in the paper.

It is a successful attempt to identify and confirm candidate gene in the sporadic CdLS patients, which inspired an idea for performing trio exome sequencing in presumed sporadic cases. It is a very tremendous task to improve gene spectrotyping in genetic disease and would also be interesting. On the other hand, the paper had illustrated a prospective of an enzymatic activity disturbed with carrying the mutations in HDAC8, and follow-up studies are required to identify recurrence or functional proof of pathogenicity. Other issues like why does the CdLS patients with the same mutated gene show different clinical manifestations, Is there other responsible genes resulting in the disease, what is the relationship between them, and does the functional mechanisms in the mutated gene refer to the embryonic development and system differentiation would be the key research directions.

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L Sun is at Department of Dermatology at No.1 Hospital, Institute of Dermatology, Anhui Medical University, Hefei, Anhui, China
E-mail: ahmusld@163.com