The importance of the clinical reanalysis of whole exome sequencing data: discovery of a pathogenic variant in the *SETD1A* gene

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Background & Objectives: As the number of genes analyzed by commercial sequencing diagnostic tests increases, interpretation of the results becomes more challenging for clinical geneticists. These studies have the potential to detect new genetic variants and their analysis is a dynamic process. In a significant proportion of cases no results are found in a first instance analysis, but if the sequencing data is re-analyzed in a certain amount of time, it is possible to encounter new findings. We present the case of a 5-year-old male patient with healthy non-consanguineous parents. He was referred to clinical genetics with a history of delayed psychomotor development, hypotonia, and dysmorphia. He has a 46,XY karyotype and a panel of 21 microdeletions without alterations. Given the suspicion of Opitz-Frias syndrome, whole exome sequencing (WES) was requested which showed a variant of uncertain significance in the *KMT2C* gene associated with Kleefstra syndrome, a phenotype that did not fit the patients' phenotype.

Method (s) and Results: We reanalyzed the VCF file from the WES performed by the commercial laboratory a year later from the initial report in the local clinical setting using free access tools. Through this exercise we found a new pathogenic variant in the *SETD1A* gene. Recent studies suggest that loss-of-function variants in *SETD1A* cause a variety of neurodevelopmental disorders that match the patient's phenotype.

Conclusions: This began as an exercise in our training process as clinical geneticists to learn how to analyze sequencing raw data, and ended up highlighting the importance of the reanalysis of the data in cases where the first report did not show conclusive findings. The study of human Mendelian diseases is ongoing and approximately 250 novel gene–disease and 9200 novel variant–disease associations are reported each year. Reexamination of sequencing data is cost-effective and may benefit patients and their families.

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