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Diagnosis of hereditary copper disorders in childhood by Next-Generation Sequencing

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Abstract

Background: Next-Generation sequencing (NGS) has opened up novel diagnostic opportunities for children with unidentified, but suspected copper inherited diseases as Wilson Disease, Aceruloplasminemia or other copper rare diseases. We describe the experience of our Reference Center for Wilson Disease and other Rare Copper Disease.

Objectives: The aim of this study was to use a panel of copper genes or modifier genes to diagnose copper rare diseases.

Materials and Methods: This study included 49 children with abnormal copper analysis. After automated DNA extraction, the DNAs were screened by NGS using a panel of genes [***ATP7B*** (NM_000053), ***Cp*** (NM_000096), ***ATOX1*** (NM_004045), ***COMMD1*** (NM_152516), ***APOE*** (NM_001302688), ***MTHFR*** (NM_005957), ***PRNP*** (NM_000311), ***XIAP*** (NM_001167), ***IL1RN*** (NM_173841), ***BDNF*** (NM_001143810), ***SLC33A1*** (NM_004733)]. Library preparations for NGS were established using a hybrid capture system for sequencing on the Miseq sequencer. The bioinformatics is performed with pipeline plateform of Hospices Civils de Lyon. All pathogenic variant were confirmed by Sanger sequencing.

Results: In 39 of these children we detected pathogenic or likely pathogenic variants in three different copper genes (*ATP7B*, *CP*, *SLC 33A1*)

Conclusions: Our multi-gene panel is a fast and comprehensive tool to diagnose inherited pediatric copper disorders. We also illustrate the challenge of dealing with genetic variants and highlight arising clinical questions, especially in patients with atypical phenotypes.