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CC8 | Clinical Genetics

Neurodegenerative Lysosomal Diseases Approached by Next Generation Sequencing

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Introduction: Lysosomal Storage Disorders (LSD) are a heterogenous group of rare, monogenic diseases with significant phenotypic overlap and clinical variability. For this reason, the diagnosis is difficult and time consuming, with multiple tests/samples being often required before a definitive diagnosis is reached. Next Generation Sequencing (NGS) is changing this scenario by allowing the variant assessment at a large scale in a single run. The aim of this work, was to develop an NGS-based workflow for the identification of LSD-causing variants.

Methods: We designed a panel including exons and intronic flanking regions from 96 genes involved in lysosome homeostasis and function. The workflow was performed using an Agilent SureSelect QXT Target Enrichment protocol followed by sequencing in an Illumina MiSeq® platform. For alignment and variant annotation the softwares Surecall and wANNOVAR were used.

Results and Discussion: To address sensitivity and coverage of this custom-targeted panel, 14 patients were analyzed. In 5 patients, used as positive controls, the disease-causing mutations had been previously identified by Sanger. For the remaining 9, we could reach molecular diagnosis consistent with the clinical and biochemical diagnosis in 5 patients. For the 4 undiagnosed patients (suspicion of LSDs), other NGS approaches are envisaged. From our results we would like to highlight the detection of a novel frameshift mutation in the GM2A gene, which is associated with an extremely rare AB variant of Gangliosidosis, biochemically and clinically undistinguishable from the other two (Tay Sachs and Sandhoff Diseases). Also noteworthy, we were able to detect the molecular defect of a patient with a clinical suspicion of Neuronal Ceroid Lipofuscinosis (CLN). From the 14 possible genes associated to these disorders, we could detect the molecular defect with a single analysis. We detected a novel missense variant in the MFSD8 gene reaching the diagnosis of a CLN7. Additionally, we have also found novel mutations in GLA, ARSB, GALC and NAGLU genes. This NGS panel that we have now available in our department offers a unique testing strategy for the LSD diagnosis, especially those for which biochemical testing is currently unavailable. Besides decreasing the delay in diagnosis for many patients, a precise molecular diagnosis is extremely important as new therapies are becoming available for patients who share specific types of mutations.

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