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Next-generation sequencing today: Genetic diagnosis, risk prediction and variant classification

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Next-generation sequencing (NGS) technology expanded in the last decades with significant improvements in the reliability, sequencing chemistry, pipeline analyses, data interpretation, and costs. Such advances make the use of NGS feasible in clinical practice today. This presentation describes the recent technological developments in NGS applied to the field of rare diseases. A number of clinical applications are highlighted i.e., variant detection of autosomal recessive diseases based on DNA-sequencing, detection of splice variants based on RNA-sequencing, application for pre-implantation genetic diagnosis, downstream variant analysis by using functional model assays. In a recent study we provided data on 3 families with the pediatric mitochondrial disease, and multiple oxidative phosphorylation deficiencies (OXPHOS), but we identified the causative variant by exome-sequencing. Given the genetic heterogeneity of OXPHOS disorders with more than 1400 nuclear genes potentially involved, Whole Exome Sequencing (WES) is the best suitable unbiased approach for finding the underlying genetic cause. First, we started with an autosomal recessive disease model and in case of reported consanguinity i.e. one patient, we focused on homozygosity regions. Conclusive remarks, clinical and technical limitations, implications and ethical considerations that relate to NGS are provided.

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