GENETIC DIAGNOSIS OF MITOCHONDRIAL DISEASES BY DETECTION OF ABERRANT EXPRESSION AND SPLICING EVENTS IN RNA SEQUENCING DATA

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Background and objective

Mitochondrial diseases (MDs) are the commonest group of inborn errors of metabolism. Genetic diagnosis is crucial for disease management but challenging owing to phenotypic and genetic heterogeneity. MtDNA sequencing and whole exome sequencing (WES) are useful diagnostic tools, but a proportion of the patients remains undiagnosed. In this study, we aim to investigate the power of RNA sequencing (RNAseq) to overcome the limitation of WES for genetic diagnosis.

Methods

We studied a cohort of 25 undiagnosed patients with suspected MDs after WES. RNAseq was undergone for the fibroblasts of these 25 patients together with 6 genetic confirmed positive controls, 2 undiagnosed patients with other diseases and 8 unaffected controls. We implemented a recently established workflow, Detection of RNA outliers pipeline (DROP), to detect aberrant expression and splicing events.

Results

A total of 95 significant expression outliers and 1847 splicing outliers have been identified in the patients. Two significant aberrantly expressed genes, *MFSD1* and *GFM1*, were found in one of the undiagnosed MD patients. These two genes are located with high proximity on chromosome 3 and a possible deletion covering *MFSD1* is suggested. Further studies are needed to investigate whether the deletion will affect cis-acting elements controlling the expression of *GFM1* associated with oxidative phosphorylation deficiency. An aberrant splicing event was identified in another patient resulting in partial intron 2 retention in *POLRMT* encoding mitochondrial RNA polymerase. Functional study is essential to evaluate the effect of the intron retention on protein function.

Conclusion

Here we have investigated a transcriptome-directed approach for molecular diagnosis of MDs. Further investigation by alternative prioritization of outliers and functional confirmation will be proceeded to identify candidate genetic defects to explain the patients' phenotypes.

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