Abstract

We present here a family whose inherited complex chromosomal rearrangements (CCR)s were evaluated using both traditional molecular cytogenetic approaches including karyotyping, fluorescence in situ hybridization (FISH), chromosome microarray analysis (CMA), as well as two novel methods including optical genome mapping (OGM) and proximity ligation sequencing (Hi-C). Both OGM and Hi-C defined the breakpoints of CCR in the proband and her mother at higher resolution than the conventional test methods. We also performed transcriptome and methylene analyses of this family, and identified the biological pathways associated with the proband’s phenotypes.

Introduction

Conventional cytogenetic tools have specific limitations with each method, such as karyotyping is a single cell whole genome assay but having limited resolutions, FISH is a targeted assay with limited coverage, and cytogenomic microarray analysis can detect CNAs and copy neutral LOH (cnLOH) with high resolution but not able to detect balanced rearrangements. Some NGS methods also have limitations, such as low pass whole genome has low resolution due to limited read length and depth [1] and not able to detect copy neutral LOH nor balanced rearrangements while long-read sequencing technology is limited by the requirement for high molecular weight DNA, relatively high error rate, lack of mature computational analysis tools and high sequencing cost [2].

OGM and Hi-C are two high-throughput technologies that capture ultra-long range contiguity information and enable precise detection of all types of SVs in a single assay. OGM, is an imaging-based method that produces DNA fingerprints spanning very large genomic regions [3]. Hi-C is a chromatin conformation analysis to capture chromatin contacts within the nucleus by proximity ligation followed by NGS [4]. Although based on different principles, both technologies potentially allow for improving test accuracy with high resolution.

We present here a family whose inherited complex chromosomal rearrangements (CCR)s were evaluated using both traditional molecular cytogenetic approaches and two novel methods, OGM and Hi-C. The indication for testing in the proband was significant intellectual disability and an immune deficiency. Her mother was unaffected. We also performed transcriptome and methylene analyses of this family, and identified the biological pathways associated with the proband’s phenotype.

Results

1. Karyotype and FISH analysis identified a CCR with at least 4 breakpoints in the proband and 7 breakpoints in her mother involving chromosomes 1, 7 and 11.

2. CMA showed a terminal duplication of 7pter-p22 and 3 interstitial deletions of 1q44, 7q11 and 11q25 in the proband but a balanced genome in her mother.

3. OGM and Hi-C defined the breakpoints and identified chromosomal configurations of CCR in the proband and her mother at high resolutions.

Methods and Materials

Here, we report on genome, transcriptome and methylene data analyses from a female patient with idiopathic thrombocytopenic purpura (ITP) and developmental delay who has an inherited complex chromosomal rearrangement. Genotype were done for the proband and her mother with conventional cytogenetic methods and two novel methods, OGM and Hi-C. The indication for testing in the proband was significant intellectual disability and an immune deficiency. Her mother was unaffected. We also performed transcriptome and methylene analyses of this family, and identified the biological pathways associated with the proband’s phenotype.

Conclusion and Discussion

• We demonstrated the use of OGM and Hi-C as tools for detection of chromosomal rearrangements and copy number alterations in constitutional disorders.

• OGM and Hi-C detected novel chromosomal rearrangements and implicated genome organizations in proband and her mother at a high resolution in addition to CCRs detected by conventional cytogenetic methods.

• This integrative study of proband’s genomics uncovered key biological pathways associated with proband’s phenotype.

References


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