**Supplementary Methods**

Three hundred nanogram of genomic DNA was extracted from peripheral blood mononuclear cells. DNA fragments were ligated with adaptors and two paired-end DNA libraries with insert size of 500 bp were formed for all samples. Fragments of patients’ genomic DNA were enriched for clinical exome sequencing (CES) using the Agilent ClearSeq Inherited Disease panel kit (Santa Clara, California, USA). DNA libraries after the enrichment were sequenced on the HiSeq2500 sequencer according to the manufacturer’s instructions (Illumina, San Diego, CA), resulting in the 150bp paired-end sequencing reads with at least 120-fold average sequencing depth for each sample.

Sequencing reads were aligned to human reference (GRCh37). Variants were called following the Genome Analysis Toolkit Best Practices Pipeline [1]. The number of reads covering each exon of the captured region was calculated from the BAM file using BedTools with its default parameters. SNVs and indels were annotated using Ensembl’s Variant Effect Predictor (VEP) and ANNOVAR followed by filtering for population frequency and consequence. The interpretation of sequence variants followed published standards and guidelines [2,3]. We built an in-home CNV detection pipeline based on CANOES and HMZDelFinder [4,5]. The provisional oral report was provided to clinicians immediately after a diagnosis was made. Genetic experts from the laboratory were invited to join the multidisciplinary consultation teams. Genetic diagnosis guided the clinical treatment strategy.

Reference

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