BMC Research Notes

RESEARCH NOTE Open Access

Rapid prenatal CNV detection using nanopore technology

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Abstract

Rapid identification of copy-number variations (CNVs) is crucial in prenatal diagnosis; however, current chromosomal microarray analysis (CMA) has a lengthy turnaround time. We evaluated the feasibility of low-pass nanopore sequencing for genome-wide CNV detection using amniotic fluid and umbilical cord blood from 22 samples. Combining the enzymatic reaction step with nanopore sequencing or the nCNV-seq technique achieved complete concordance with CMA across all abnormal and normal cases, accurately detecting CNVs as small as 0.7 Mb. The workflow generated > 1 million reads per sample, providing sufficient coverage (< 1×) for reliable CNV profiling. These findings demonstrate that nanopore sequencing can serve as an alternative to CMA for rapid testing, potentially lower investment costs, and faster turnaround times.

Keywords Aneuploidy, Amniotic fluid, Anomaly, Cord blood, Nanopore, Copy number variations, CNV, Prenatal diagnosis, Long read sequencing, Bioinformatics

Introduction

Aneuploidy and chromosomal abnormalities are major causes of miscarriage, fetal structural anomalies, and developmental delay [1, 2]. Early identification of genetic abnormalities is a crucial step in prenatal care. The standard comprehensive genetic assessment includes G-banded karyotyping and chromosomal microarray analysis (CMA) [3, 4]. The latter method enables detection of copy number variation (CNV) with a size of approximately 50–100 kb [5], whereas the former method can detect CNVs larger than 5 Mb. Previous reports have shown that the use of CMA increases the additional yield of CNV detection by 1.7-6% for the identification of prenatal genetic diseases [5]. Therefore, the use of CMA is recommended as the primary test (replacing conventional karyotyping) for fetal structural abnormalities detected by ultrasound, according to professional

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organizations [4, 6, 7]. The drawbacks of the CMA are that it requires complex DNA library preparation and state-of-the-art equipment, and the array platform is not designed to run a single sample at a time. Importantly, its turnaround time is 7–10 days, restricting its clinical management and decision-making.

Recently, third-generation sequencing technology, such as that developed by Oxford Nanopore Technologies (ONT), has gained momentum [8]. This technology has improved significantly, with a low sequencing error rate (percentage of unmatched bases in the DNA alignment) of less than 3.5% [9–11]. Importantly, nanopore sequencing enables real-time analysis with same-day results and can be initiated at any time, as the MinION sequencer is a miniature, palm-sized device [12–13]. Our group has reported the potential clinical applications of nanopore sequencing, including the rapid diagnosis of intraamniotic infection [14–16] and the determination of complete bacterial genomes associated with intraamniotic infection [17–20]. In addition, Wongsurawat et al. showed that nanopore sequencing enables genome-wide copy number variation (CNV) profiling in brain tumors, and this service is now being implemented in Thailand [21]. Together, these findings highlight the strong potential of nanopore sequencing to detect structural genomic alterations, such as CNVs, for clinical management. Building on this potential, we hypothesize that nanopore sequencing could also address unmet diagnostic needs in prenatal testing, where the detection of small pathogenic microdeletions (< 1 Mb) remains particularly challenging. If CNV detection can be achieved in the context of prenatal diagnosis—which poses additional challenges due to the small size of pathogenic microdeletions—it could enable rapid identification of clinically significant microdeletion syndromes. This study aims to determine whether nanopore sequencing can detect genome-wide CNVs in prenatal diagnosis, compared to conventional CMA.

Methods

Study design

This study includes both retrospective and prospective components. The prospective component study comprised pregnant women who underwent prenatal genetic testing at Ramathibodi Hospital, Bangkok, Thailand, from March 2024 to March 2025. The inclusion criteria were defined as singleton pregnant women aged 18 years or older whose amniotic fluid or umbilical cord blood was collected for prenatal genetic testing, as recommended by the American College of Obstetricians and Gynecologists [4], including (1) Advance maternal age (2) Parental carrier of chromosome rearrangement (3) Parental aneuploidy or aneuploidy mosaicism (4) Prior child with structural birth defect (5) Parental carrier of a genetic disorder (6) Previous fetus or child with autosomal trisomy or sex chromosome aneuploidy (7) Structural anomalies identified by ultrasonography, with both karyotyping and chromosomal microarray results available. We excluded patients who refused prenatal genetic testing or refused to participate in the study. Each patient provided written informed consent before sample collection, and the use of biological specimens and clinical data for research purposes was approved by the Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (COA. MURA 2023/628). For the retrospective component, we selected prenatal samples from the Human Genetic Laboratory biobank and the Ramathibodi Comprehensive Tumor Biobank, including amniotic fluid, umbilical cord blood, and post-abortion tissue, as available from January 2020 to August 2024. The use of leftover specimens for research purposes was approved by the Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University (COA.MURA 2024/541). The experimental workflow is shown in Fig. 1.

The participants are classified into 2 groups: (1) The control group included patients with a normal karyotyping and chromosomal microarray results ($n = 13$), and (2) The cases group included those with either a positive karyotyping or chromosomal microarray results ($n = 9$).

Genomic DNA (gDNA) extraction and quality measurement

According to the manufacturer's protocol, gDNA was extracted from amniotic fluid or umbilical cord blood using a DNA purification kit (GenEx™ Blood Kit; GeneAll Biotechnology, Korea). The acceptable DNA quantity and quality criteria include (1) at least 1 µg of gDNA, (2) the OD 260/280 ratio between 1.8 and 2.0, and (3) the average fragment size, as measured by agarose gel analysis, greater than 20 kb.

Library preparation and Oxford nanopore sequencing

Rapid prenatal CNV detection was performed using the nCNV-seq protocol, which was optimized for Oxford Nanopore sequencing (ONT, UK) [21, 22]. The protocol consisted of four main steps. First, genomic DNA extracted from prenatal samples was digested using the restriction enzyme Anza™ 64 SaqAI (Thermo Fisher Scientific, USA) at 37 °C for 30 min to generate defined fragment ends. Second, the digested DNA was purified using the Monarch® PCR & DNA Cleanup Kit (New England Biolabs, USA), which involves binding to a silica membrane, followed by ethanol-based washes and elution in nuclease-free water. In the third step, the cleaned DNA was re-ligated using Anza T4 DNA Ligase Master Mix (Thermo Fisher Scientific, USA) and incubated at room temperature for 30 min to promote intramolecular ligation and circularization. Fourth, a bead-based cleanup was performed using AMPure XP beads (Beckman

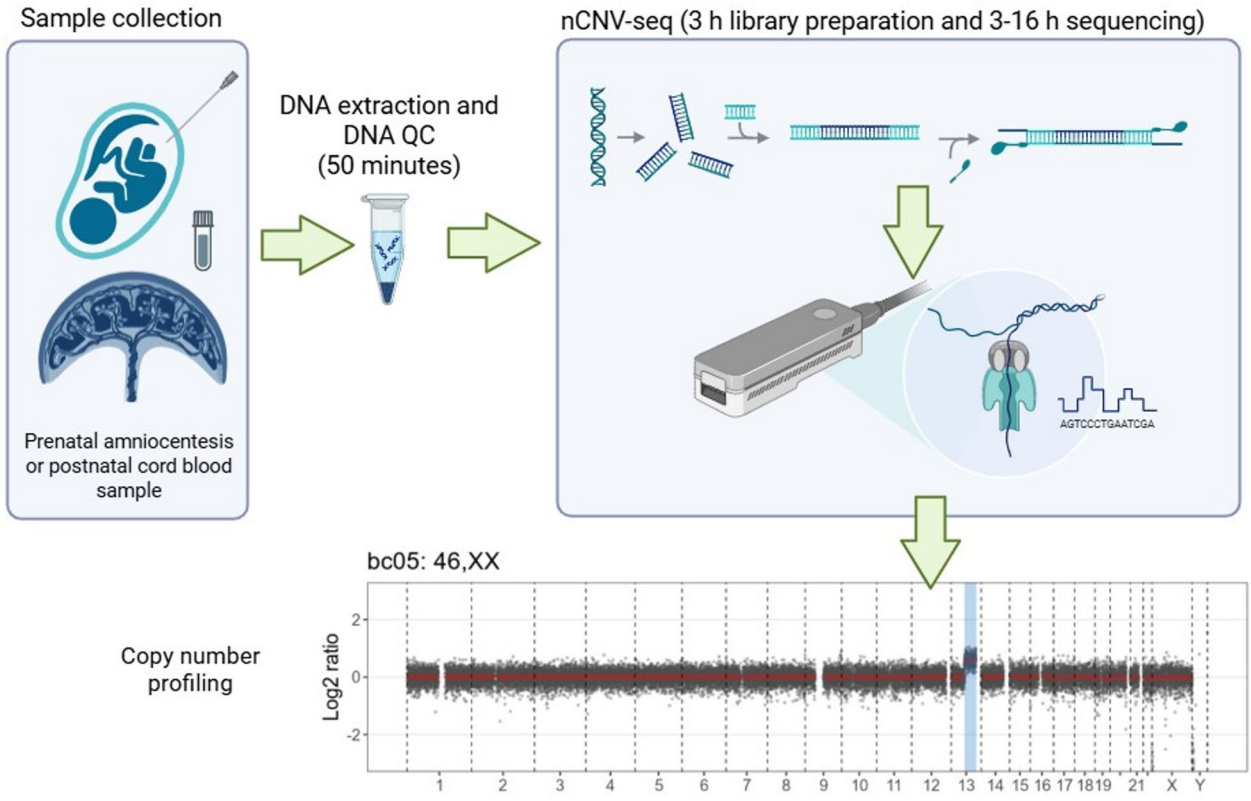

Fig. 1 Experimental workflow of CNV detection using short-read Nanopore sequencing. Prenatal amniocentesis or postnatal cord blood sampling was done in high-risk pregnancies for fetal genetic abnormalities. gDNA extraction was done from amniotic fluid or cord blood. The leftover gDNA was shared from the clinical genetic lab in retrospective cases. DNA library preparation and long-read sequencing (nCNV-seq) were performed in the Nanopore sequencing lab. From gDNA extraction to Real-time data analysis for CNV detection was completed within 1–2 days. The relative copy-number plots across 24 chromosomes showed a predicted trisomy 13. CNV, copy number variation

Coulter, Inc., USA), including sequential ethanol washes (molecular grade) and elution in nuclease-free water to obtain high-purity ligated DNA. Library preparation was then completed using Oxford Nanopore's Rapid Barcoding Kit, RBK114.24 (ONT, UK), involving transposase-based fragmentation and barcoding, followed by adapter addition. The prepared library was loaded onto a MinION flow cell (FLO-MIN114, ONT, UK), enabling real-time nanopore-based CNV analysis.

Bioinformatics analysis

The raw sequencing data were processed using Dorado v0.7.3 for base-calling and demultiplexing [https://github.com/nanoporetech/dorado], followed by adapter trim ming with Porechop v0.2.4 [https://github.com/rrwick/Porechop]. High-quality reads were subsequently aligned to the hg38 human reference genome using minimap2 v2.28-r1209 [23] with the parameters -x map-ont --secondary = no to suppress secondary alignments.

For copy number variation (CNV) analysis, we employed the QDNAseq R package [24], which is optimized for CNV detection from low-pass whole-genome sequencing data. The pipeline partitions the hg38 reference genome into fixed bins of 100 kb and extracts read counts per bin from the aligned BAM files. Counts were normalized to correct for GC-content, mappability biases, and blacklisted regions. To further improve data quality, centromeric and flanking regions were excluded from analysis. Finally, scatter plots were generated using R to visualize the copy number profiles, and reproducibility of the copy number levels (log2 ratio) was assessed.

Results

The clinical characteristics of the participants are demonstrated in Tables 1 and 2. A total of 22 samples were obtained. Among the 22 samples, 16 samples (14 amniotic fluid, 2 umbilical cord blood) were collected from a prospective cohort, while the remaining 6 samples were derived from a biobank of the genetic laboratory unit. Indications for prenatal or postnatal diagnosis were fetal anatomical abnormalities, fetal growth restriction, advanced maternal age, or positive non-invasive prenatal tests.

Among the 22 cases, 9 were classified into the case group and 13 into the control group. In the case group, nanopore sequencing demonstrated complete

Table 1 Comparison of CNV detection between karyotype /CMA and Nanopore sequencing results in the case group

Case	Specimen	Indications for PND	Karyotype/CMA results	Nanopore results	CNVs interpretation	Genome Coverage (X)	No. of mapped reads
1	Leftover DNA	severe FGR, microcephaly	4q34.1dup (15.9 Mb) 3p25.3del (8.4 Mb)	4:175000001-190800000 dup (15.8 Mb) 3:100001-8500000 del (8.4 Mb)	Pathogenic	0.17	1,828,828
2	Leftover DNA	cleft palate, pulmonary stenosis with VSD	10q22.3-q23.2del (7.14 Mb)	10:81800001-88800000 del (7 Mb)	Pathogenic	0.26	2,885,507
3	Leftover DNA	bronchopulmonary sequestration	15q11.2 dup (0.86Mb)	15:19700001-20500000 dup (0.8Mb)	VUS	0.18	1,970,402
4	Amniotic fluid	cleft lip, polydactyly, bilateral UTD	13q21.34 dup (43.92 Mb)	13:712000001-115169878 dup (43.97 Mb)	Pathogenic	0.15	1,677,052
5	Cord blood	High-risk for T21 from NIPT	47, XX+21	47, XX+21		0.29	3,269,246
6	Amniotic fluid	High-risk NIPT for 47, XXY	47, XXY	47, XXY		0.13	1,320,225
7	Leftover DNA	Pulmonary atresia with VSD	22q11.21 del (2.62 Mb) 8q21.13 (2.1 Mb)	22:19000001-21500000 del (2.49 Mb) 8:83300001-85400000 del (2.1 Mb)	Pathogenic	0.38	3,281,666
8	Leftover DNA	ACC with thick nuchal fold	22q11.21q11.23 del (0.7 Mb)	22:22700001-23300000 del (0.6Mb)	Pathogenic	0.60	5,861,205
9	Leftover DNA	DORV, cardiomyopathy	22q11.21 del (3.15 Mb)	22:19000001-21500000 del (2.49 Mb)	Pathogenic	0.82	7,807,505

PND prenatal diagnosis, *CMA* chromosomal microarray, *FGR* fetal growth restriction, *VSD* ventricular septal defect, *UTD* urinary tract dilatation, *NIPT* non-invasive prenatal test, *ACC* agenesis of corpus callosum, *DORV* double outlet right ventricle, *VUS* variant of unknown significance.

Table 2 Comparison of CNV detection between karyotype/CMA and Nanopore sequencing results in the control group

Case	Specimen	Indications for PND	Karyotype/CMA results	Nanopore results	Coverage	No. of mapped reads
10	Amniotic fluid	Sacrococcygeal teratoma	46, XY	46, XY	0.23	2,577,046
11	Cord blood	ARPKD, polydactyly	46, XY	46, XY	0.1	1,086,349
12	Amniotic fluid	Thick nuchal translucency	46, XX	46, XX	0.23	2,505,096
13	Amniotic fluid	Meningomyelocele	46, XX	46, XX	0.42	1,336,274
14	Amniotic fluid	Fetal growth restriction	46, XY	46, XY	0.53	2,074,720
15	Amniotic fluid	Large bowel obstruction	46, XY	46, XY	0.37	3,886,694
16	Amniotic fluid	Risk for major thalassemia disease	46, XX	46, XX	0.37	3,824,935
17	Amniotic fluid	Fetal growth restriction	46, XY	46, XY	0.54	5,500,621
18	Amniotic fluid	Advanced maternal age	46, XX	46, XX	0.20	2,067,942
19	Amniotic fluid	Advanced maternal age	46, XX	46, XX	3.31	33,528,431
20	Amniotic fluid	Unilateral cleft lip/cleft palate	46, XY	46, XY	0.54	6,024,634
21	Amniotic fluid	Positive Down syndrome screening	46, XY	46, XY	0.51	5,582,832
22	Amniotic fluid	Thick nuchal translucency	46, XX	46, XX	0.47	4,749,003

ARPKD autosomal recessive polycystic kidney disease.

concordance with chromosomal microarray results in all 9 cases (shown in Table 1). These included one case of trisomy 21, one case of sex chromosomal aneuploidy (47, XXY), six cases of pathogenic CNVs, and one case of a variant of unknown significance (VUS) CNV, with sizes ranging from 0.7 to 43.92 Mb. In the control group (shown in Table 2), the nanopore sequencing results were likewise concordant with those from chromosomal microarray, confirming normal findings in all 13 cases. The representative profiles were illustrated in Supplementary Fig. 1. Sequencing runs yielded 1–2 Gb per sample, corresponding to low-pass whole-genome coverage (coverage < 1× on average), which is sufficient for robust CNV detection in our pipeline.

Discussion

This study demonstrates the feasibility of low-pass nanopore sequencing as a rapid approach for prenatal CNV detection. We show that this method can reliably identify CNVs larger than approximately 0.7 Mb, with detected variants classified as pathogenic or variants of unknown significance (VUS) according to the American College of Medical Genetics and Genomics (ACMG) guidelines [25, 26]. These findings support the potential role of nanopore sequencing as a time-efficient alternative to conventional

chromosomal microarray analysis (CMA) in prenatal diagnosis, particularly in time-sensitive clinical contexts.

We would like to highlight the technical and analytical limitations of the current workflow, in which two positive cases initially resulted in negative results (Cases No. 3 and No. 8). In Case No. 3, a 0.86 Mb CNV was classified as a VUS. VUS are reported in approximately 5–6% of prenatal microarray analyses and remain challenging for clinical interpretation due to incomplete genotype–phenotype correlations and limited supporting evidence at the time of testing [27, 28]. In Case No. 8, a 0.7 Mb deletion encompassing disease-causing genes was ultimately interpreted as pathogenic despite its small size. In both cases, the small CNVs were located near heterochromatin regions that were excluded from the predefined regions of interest, resulting in initial non-detection. These observations underscore the importance of optimizing analytical parameters and coverage strategies, particularly for CNVs in complex genomic regions.

Current CMA reporting practices commonly exclude small deletions and duplications of less than 1 Mb to minimize VUS reporting, which can complicate prenatal counseling and management [29, 30]. However, this assumption does not always hold when dosage-sensitive or disease-associated genes are involved [31]. A previous study using prenatal short-read CNVseq detected the smallest CNV, 0.3 Mb, interpreted as a VUS. Whereas the smallest pathogenic variant identified was 1.4 Mb [28]. Our CNV detection results are comparable and demonstrate that low-pass nanopore sequencing can also detect clinically relevant CNVs below conventional reporting thresholds. This approach may expand the diagnostic scope of prenatal testing when combined with appropriate interpretation frameworks, while offering shorter turnaround times of 10–14 days and 1–2 days, respectively.

Previous studies have demonstrated the utility of nanopore sequencing in reproductive genetics, primarily for detecting chromosomal aneuploidy in preimplantation and prenatal samples, as well as for rapid genomic diagnostics in neonatal intensive care settings [13, 32–36]. Our results extend these applications to prenatal CNV detection and are consistent with our prior work using nanopore sequencing for rapid molecular diagnostics in infectious disease and oncology [14, 15, 17, 19, 21]. Collectively, these findings support the broader clinical potential of nanopore sequencing. A major advantage of nanopore sequencing is its real-time data generation, enabling substantially shorter turnaround times compared with CMA, which typically requires 7–10 days [37]. Rapid results may reduce parental anxiety and facilitate timely clinical decision-making, including the option for additional genetic testing when indicated.

Our study revealed that nanopore sequencing enables accurate genome-wide detection of copy number variants smaller than 1 Mb, with a current lower detection limit of approximately 0.7 Mb. Future studies will focus on identifying CNVs below 0.5 Mb and expanding the study cohort to enhance analytical sensitivity and generalizability. For time-critical CNV testing, nanopore sequencing offers potential cost advantages over array comparative genomic hybridization, while providing substantially shorter turnaround times. However, data analysis currently requires specialized bioinformatics expertise, including customized pipelines, quality control, and variant interpretation. Ongoing efforts aim to streamline analysis by further validating and automating workflows to facilitate routine clinical implementation.

Limitations

This study has several limitations. First, the sample size was small, limiting generalizability and precluding robust estimation of sensitivity and specificity, particularly for small CNVs. Larger cohorts will be required to validate diagnostic performance and define reliable detection thresholds. Second, two potentially pathogenic CNVs were initially missed due to their proximity to heterochromatin regions outside predefined regions of interest, highlighting limitations in coverage and bioinformatic analysis and indicating a risk of false-negative results. Third, the cohort did not include certain CNV types that are challenging for CMA, such as mosaic variants or hemizygous deletions. These variants are clinically important, as they may underlie severe disorders, including Duchenne muscular dystrophy. Finally, this study is a proof-of-concept, retrospective study, which limits the ability to directly establish clinical equivalence between nCNV-seq using nanopore sequencing and CMA. Future studies incorporating larger prospective cohorts, optimized pipelines, and direct clinical comparisons are necessary before routine implementation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13104-026-07818-2.

Supplementary Material 1. Fig. 1. Whole-genome scatter plot demonstrated CNV in prenatal specimens. (A) 46, XX (B) 46, XY (C) 22q11 deletion (22:22700001–23300000) (0.6 Mb). CNV, copy number variation.

Acknowledgements

TW's project was partially supported by the Faculty of Medicine Siriraj Hospital, Mahidol University, Project No. R016841003.

Author contributions

MB, PC, and TW conceived of and designed the study. MB applied for IRB approval. MB, PC, PW, and MP recruited patients and obtained informed consent. Clinical samples were processed by MB and SH. PC supported the initial study to develop the method and edited the manuscript. MB and SH extracted DNA and handled samples. Leftover DNA was courtesy of BR, RP, TC,

WT, and NJ. TA, PN, SA, and SK prepared DNA libraries, performed nanopore sequencing. Bioinformatic analysis and interpretation were executed by PJ, TA, PN, SA, and SK. MB, PC, TA, PJ, and TW contributed to the manuscript structure. All authors reviewed the manuscript.

Funding
Open access funding provided by Mahidol University. This study was supported by the Research Fund, Faculty of Medicine Ramathibodi Hospital (RF_67118) and the Faculty of Medicine Siriraj Hospital, Mahidol University, Grant No. R016841003. The funder had no role in the design, data collection, data analysis, and reporting of this study.

Data availability
The human genomic data generated in this study have been deposited in the Genome Sequence Archive for Human (GSA-Human) at the China National Center for Bioinformation under accession number HRA016439. Access to these data is controlled due to ethical and privacy considerations and is available to qualified researchers upon reasonable request through the GSA-Human Data Access Committee.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the Mahidol University Multi-faculty Cooperative IRB committee, Mahidol University, approval number MURA2024/541, and Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, approval number MURA2023/628. Informed consent to participate was obtained from the patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 9 January 2026 / Accepted: 2 April 2026
Published online: 12 April 2026

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