HiFi long-read
Whole Genome Sequencing (HiFi LR-WGS)

Unlock answers that were previously out of reach

Over 7,000 rare diseases affect more than 300 million people worldwide, with about 80% having a genetic origin. [1] While short-read whole exome sequencing (WES) or whole genome sequencing (WGS) are commonly used to identify genetic factors, these methods provide answers in only about 30–40% of cases. A key limitation is that short-read sequencing has limited variant detection, such as structural variants and mutations in low-mappability regions.

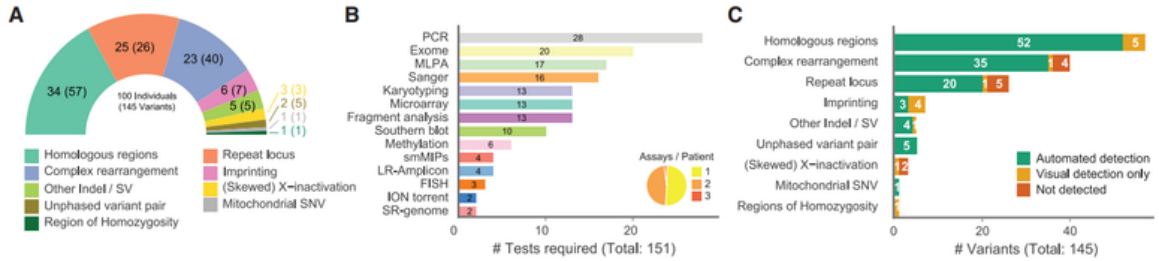
HiFi Long-read whole genome sequencing (HiFi LR-WGS) with PacBio SMRT technology overcomes these challenges, offering comprehensive mapping and superior accuracy for variant detection.

HiFi LR-WGS shows an improved diagnostic rate

Technology	Explanation Rate
Chromosomal microarray analysis (CMA)	~10%
Short-read WES	~30 – 40%
Short-read WGS	~40%
HiFi LR-WGS	**>50%**

Information derived from reference [2-4]

Long-read identifies more variants than short-read in one step



A) Distribution of variant type that are challenging or impossible to identify by short-read WGS but further confirmed by additional assays
B) Additional assays used to identify; Pie chart illustrated number of assays required per patient
C) The capability of HiFi LR-WGS on identify those variants; Green: Variant caller; Orange: Visual read inspection; Red: Undetected
Figure adopted from reference [5]

The technical limitations of short-read sequencing can lead to missed variants and so-called 'unsolved cases'. complicating and prolonging the diagnostic process (requiring one or more additional assays). **HiFi LR-WGS offers a comprehensive, one-stop solution, reducing missed variants by over 93% and significantly improving diagnostic yield.**

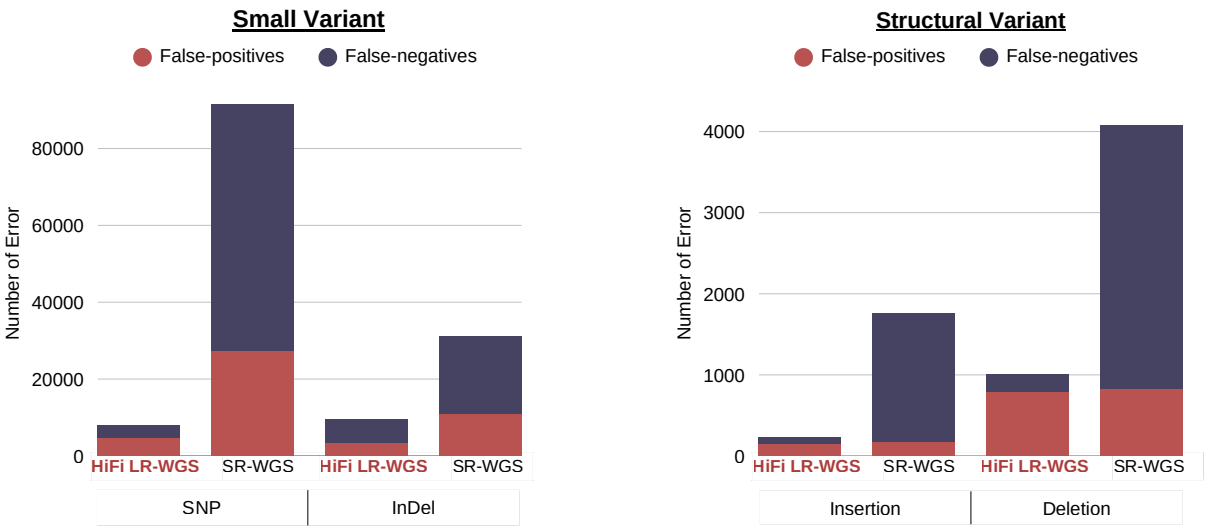
Type of variant		Karyotyping	CMA	CNV-seq	Short-read WES	Short-read WGS	HiFi LR-WGS
SNV/InDel	Exon	-	-	-	✓*	✓*	✓
	Deep intronic	-	-	-	Limited	✓*	✓
	Intergenic region	-	-	-	Limited	✓*	✓
SV	Insertion	-	-	-	-	Limited	✓
	Inversion	✓	-	-	-	Limited	✓
	Balanced translocation	5Mb	-	-	-	✓	✓
	Non-balanced translocation	5Mb	✓	✓	-	✓	✓
CNV	Duplication/deletion	-	100kb	100kb	Limited	>50bp	>50bp
Methylation	Imprinting		-	-	-	-	✓
Tandem repeat	Repeat number	-	-	-	Limited	Limited	✓
Mitochondria	SNP/SV	-	-	-	✓	✓	✓
Variant in complex region	CNV	-	-	-	-	Limited	✓
Aneuploidy	Aneuploidy	✓	✓	✓	✓	✓	✓
	Mosaic aneuploidy	-	30%	10%	15%	15%	15%
ROH/UPD	ROH	✓	5Mb	-	Limited	✓	✓
	ROH	-	5Mb	-	Limited	✓	✓
	UPD	-	✓	-	✓	✓	✓

* Interfered by homologous regions and GC content.

Pioneers in PacBio SMRT sequencing in clinical services

Berry Genomics is one of the leading providers of clinical genetic services and the first to offer long-read genetic testing for clinical applications (e.g., thalassemia, congenital adrenal hyperplasia). Transitioning from panel tests to comprehensive genome-wide analysis, we deliver long-read WGS based on PacBio SMRT technology. This enables researchers to discover more genetic variants, especially those missed by current short-read technologies, with best-in-class reliability.

A new standard of accuracy with long-read



Internal comparison data: WGS variant calling accuracy measured as false-positives (red) and false-negatives (blue) with reference HG002 (35x, benchmark NISTv0.6)

HiFi LR-WGS demonstrates **a significant reduction in false calls** compared to short-read WGS (SR-WGS).

Furthermore, many medically relevant genes are found in complex regions of the genome, where high homology and repetitive sequences make variant detection difficult with short-read WES/WGS.

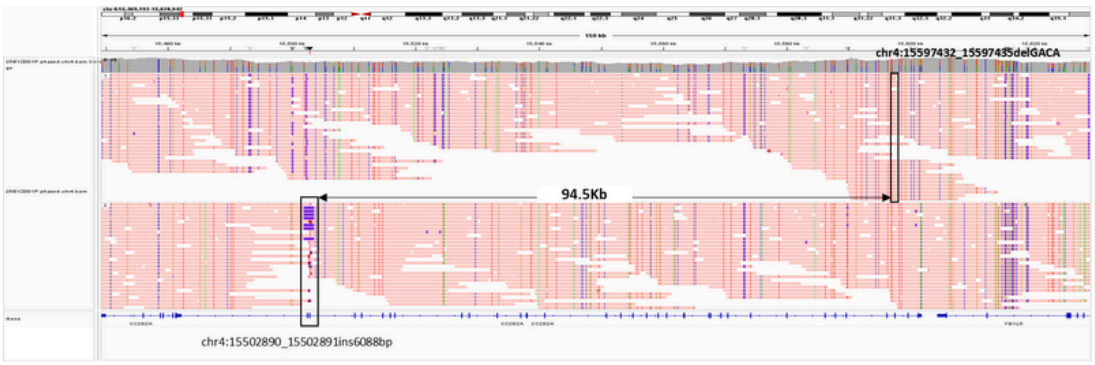
HiFi LR-WGS, using PacBio SMRT sequencing, **offers superior accuracy in these regions** and reduces missed variants.

Example of clinically relevant genes located in the complex regions:

- *SMN1*/ *SMN2* (Spinal Muscular Atrophy)
- RCCX module
  - *CYP21A2* (21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia)
  - *TNXB* (Ehlers-Danlos Syndrome)
  - *C4A*/ *C4B* (Relevant in Autoimmune Diseases)
- *PMS2* (Lynch Syndrome)
- *STRC* (Hereditary Hearing Loss and Deafness)
- *IKBKG* (Incontinentia Pigmenti)
- *NCF1* (Chronic Granulomatous Disease and Williams Syndrome)
- *NEB* (Nemaline Myopathy)
- *F8* (Inversion, Hemophilia A)
- *CFC1* (Heterotaxy syndrome)
- *OPN1LW*/ *OPN1MW* (Color Vision Deficiencies)
- *HBA1*/ *HBA2* (Alpha-thalassemia)
- *GBA* (Gaucher Disease and Parkison's Disease)
- *CYP11B1*/ *CYP11B2* (Glucocorticoid-remediable Aldosteronism)
- *CFH*/ *CFHR1*/ *CFHR2*/ *CFHR3*/ *CFHR4* (Large deletions/duplications, Atypical Hemolytic Uremic Syndrome and Age-related Macular Fegeneration)

Important: Due to the continuous improvement of the service, the data presented may change over time.

Haplotype phasing



Internal data: *CC2D2A:* c.4465_4468del(Exon36)/c.418_419insL1HS, *in trans*

HiFi LR-WGS enables the identification of ***cis or trans*** configuration of variants **without family linkage.**

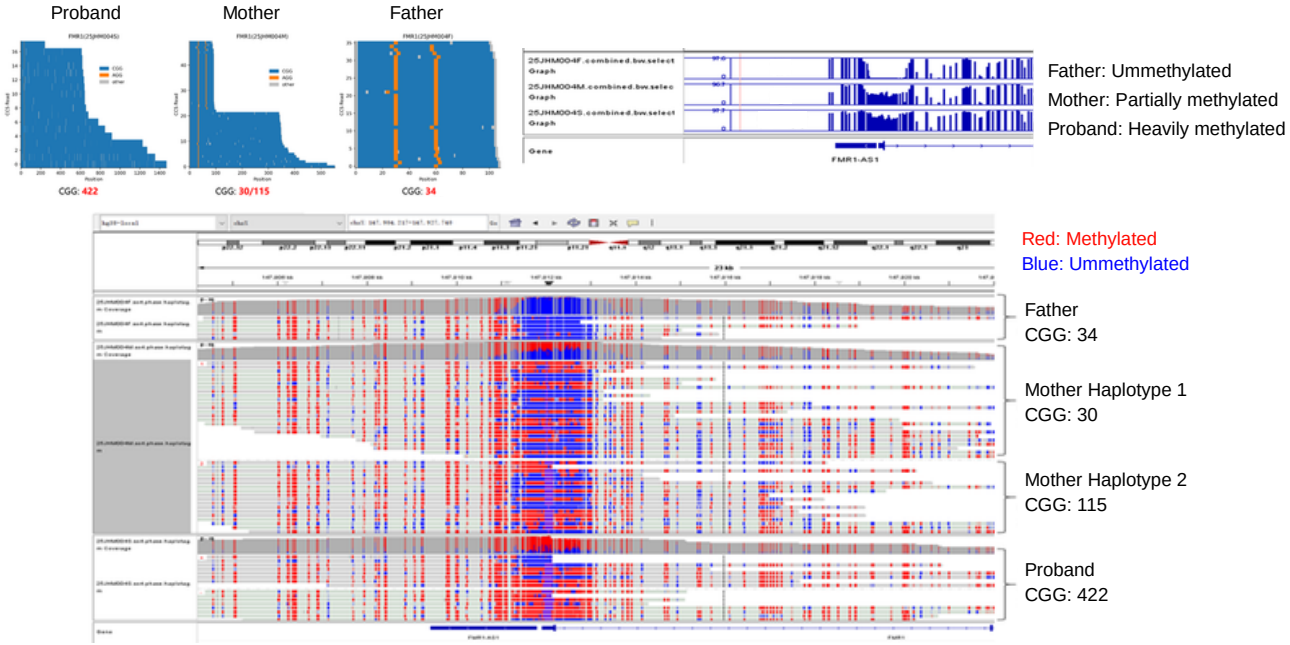
Tandem repeat and methylation

Patients with less common tandem repeat disorders are often difficult to diagnose due to high phenotypic variability and significant symptom overlap with other conditions. Relying on phenotype alone is challenging, and conventional methods cannot screen all loci or suspected genes simultaneously, often resulting in delayed diagnosis.

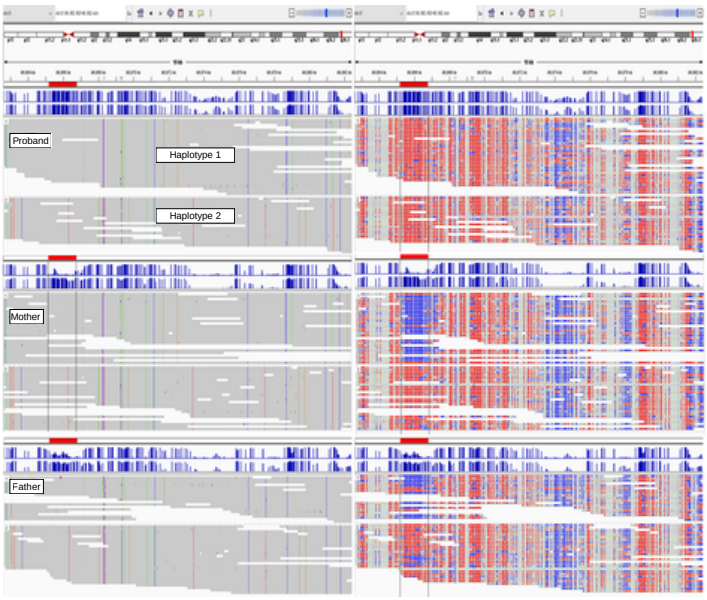
Detection capabilities of different assays

	Southern blot	RP-PCR	Short-read	HiFi read
Extreme GC content	✓	✓	×	✓
Interruptive motifs	×	×	×	✓
Large repeat units (VNTR)	✓	×	×	✓
Number of gene per assay	1	1-10	10-30	**63** (Up to date)
Repeat count accuracy	Low	Low (Limited to count <200)	Low (Limited to size <150 bp)	**High**

HiFi LR-WGS can detect cases involving repeat expansion that were previously hard to identify, without needing linkage data or prior assumptions. It also provides accurate **methylation** and **phasing** information in a single test, **outperforming short-read WGS by allowing comprehensive screening** for uncertain cases.



Internal data: *FMR1* analysis within a family by HiFi LR-WGS



Red: Methylated
Blue: Ummethylated

Haplotype and UPD analysis in HiFi LR-WGS confirmed that both copies of chromosome 15 in the proband are maternal in origin. Additionally, heavy methylation was observed in both haplotypes.

Together, these findings confirm Prader-Willi syndrome in the proband.

Internal data: Prader-Willi syndrome region methylation abnormality and maternal uniparental disomy analysis by HiFi LR-WGS

Test Information

Sample Requirement: Collect 2 mL of blood in an EDTA tube. Transport at -80 °C within 5 days or 4 °C within 72 hours. gDNA is accepted, but prior evaluation is required.
Technology: PacBio SMRT sequencing
Coverage: ≥97.5% coverage at a mean depth of 10x / 20x
Test Design: Proband, Duo or Trio analysis; Raw data; Reanalysis; Customized reporting
Turnaround Time: 34 working days

Variants Reported Associated with the Provided Phenotype

- Single-nucleotide variants (SNVs)/ Insertions and deletions (InDels)
- Copy number variations (CNVs)
- Structural variations (SVs)
- Absence of heterozygosity (AOH) / Uniparental disomy (UPD, for Trio only)
- Mitochondrial mutations (SNVs/InDels)
- Tandem repeats/Dynamic variants in 63 clinically relevant genes
- Methylation abnormalities for 8 diseases
- ACMG secondary findings

For details, please contact **marketing@xcelom.com**

Website (Global)

LinkedIn

References: [1] Rare Genetic Diseases. *National Institutes of Health*. Accessed June, 2025. https://www.genome.gov/dna-day/15-ways/rare-genetic-diseases [2] Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom Med*. 2018;3:16. Published 2018 Jul 9. [3] Wright CF, FitzPatrick DR, Firth HV. Paediatric genomics: diagnosing rare disease in children. *Nat Rev Genet*. 2018;19(5):253-268. [4] Farrow, Emily et al. O24: Unveiling the power of HiFi genome sequencing: One test to rule them all? *Genetics in Medicine Open.* Volume 2, 101471. [5] Höps W, Weiss MM, Derks R, et al. HiFi long-read genomes for difficult-to-detect, clinically relevant variants. *Am J Hum Genet*. 2025;112(2):450-456.

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