

Mahi-mahi: detect repeat expansions without repeat experiments

Resolve what was hidden

Repeat expansions are associated with over 50 rare diseases, including Huntington's disease, Friedreich's ataxia, and fragile X syndrome¹. Accurate characterisation of these sequences is paramount in the development of new methods to support diagnosis, prognosis, and effective management of repeat expansion disorders. However, characterising potentially pathogenic expansions can be complex. This may require not only measurement of the length of a repeat, but also the motifs it comprises, its methylation status and, critically, the specific allele affected.

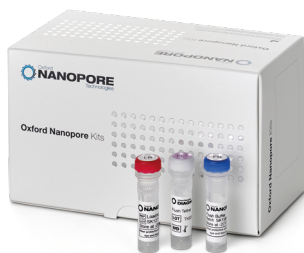
Here, we introduce Mahi-mahi²: an analysis tool that delivers thorough repeat expansion characterisation. Unrestricted Oxford Nanopore read lengths span full repeat sequences, providing haplotype-level identification of expansions that legacy short-read methods can struggle to accurately resolve^{3,4}. Powered by long nanopore reads, Mahi-mahi captures and phases repeat lengths, motifs, sequence interruptions, and methylation in a single assay.

With Mahi-mahi and our end-to-end human variation workflow, access the resolution you need to further your rare disease research.

The Oxford Nanopore workflow

1. Prepare

Extract DNA, then preserve long fragments and epigenetic modifications with PCR-free library preparation



2. Sequence

Generate high outputs at the scale you need with the PromethION™ range



3. Analyse



EPI2ME



> Mahi-mahi

Call and phase SNVs, SVs, CNVs, and methylation with wf-human-variation⁵

Call and phase repeat expansions and methylation

Mahi-mahi inputs:



Aligned data output by EPI2ME



Human genome reference



Catalogue of loci

Mahi-mahi outputs including:



Per-locus/per-allele repeat expansion calls



Per-read repeat statistics



Read-level annotations for visualisation



Per-locus motif and methylation plots (optional)

Our comprehensive workflow begins with extraction and preparation of native DNA, followed by sequencing on a PromethION Flow Cell. You can target repeats in real time with the software-based technique Adaptive Sampling* or use whole-genome sequencing. MinKNOW™, the software that controls Oxford Nanopore sequencing devices, begins analysis by basecalling your data in real time.

Next, the intuitive EPI2ME™ workflow, wf-human-variation, calls and phases single nucleotide variants (SNVs), structural variants (SVs), copy number variants (CNVs), and methylation. Finally, the command-line tool Mahi-mahi uses the aligned data output by this workflow to produce allele-specific repeat expansion lengths, motifs, and methylation, including annotations and visualisations.



Get repeat lengths, motifs, and methylation — in one go



Gain allele- and read-specific repeat expansion insights



Scale from one repeat to whole-genome insights with a single tool



Access SNVs, SVs, and CNVs from the same dataset

Don't let read length limit repeat length

To benchmark the performance of Mahi-mahi, we sequenced 24 human genomic DNA research samples and analysed repeat expansions.

Here, data is shown for selected samples that featured expanded alleles. The haplotype-level information allows clear resolution of full expansions, not only by repeat length, but also motif composition. This demonstrates the potential of this technique to resolve complex rare disease-associated variants, as well as carrier status in recessive conditions.

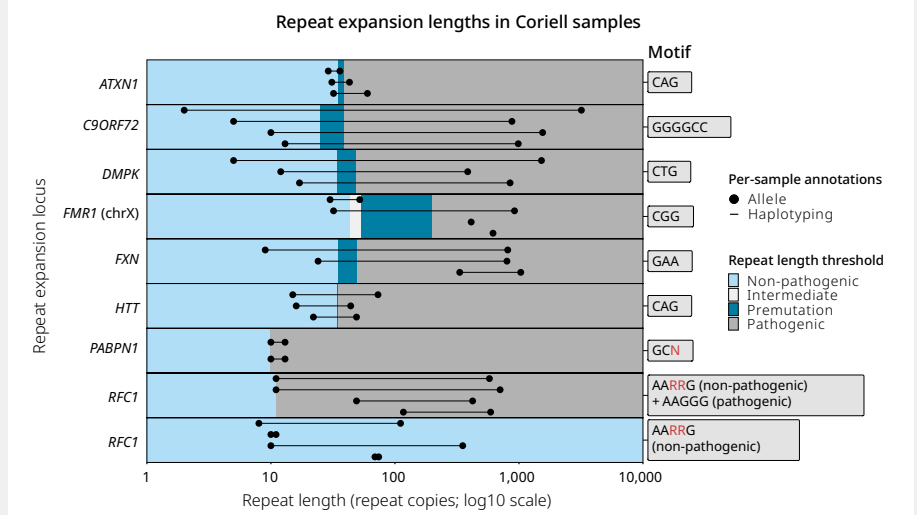


Figure 1. Mahi-mahi enables comprehensive repeat expansion analysis in human research samples. We prepared a selection of human DNA research samples⁶ using the Ligation Sequencing Kit, then sequenced on PromethION Flow Cells and analysed the data with wf-human-variation and Mahi-mahi. For some samples, repeats at more than one locus are shown. For *RFC1*, both repeat length and motif information are required to accurately determine pathogenicity; pathogenic and non-pathogenic motifs are grouped. Motif base key: 'N' = A, C, G, or T; 'R' = A or G.

Access allele- and read-specific repeat expansion analysis

In one research sample, we used Mahi-mahi to characterise repeat expansions in the gene *HTT*. Trinucleotide 'CAG' repeat expansions at this locus are associated with Huntington's disease.

This per-read visualisation of each allele demonstrates how nanopore reads deliver unambiguous identification of the expanded allele, as well as resolving the motifs present. In this autosomal dominant condition, these findings suggest pathogenic status.

Mahi-mahi also outputs methylation data visualisations, allowing analysis of repeat expansion lengths, motifs, and methylation from the same data.

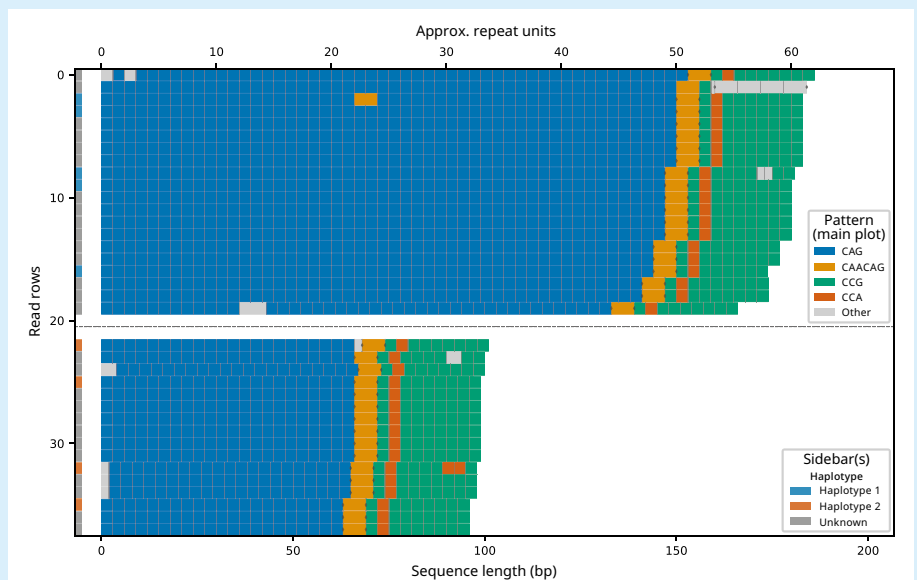


Figure 2. Mahi-mahi delivers allele- and read-specific repeat expansion information and visualisation. In this example, nanopore reads allow clear haplotype phasing of the *HTT* locus, showing one expanded allele and the motifs present. The left-hand column indicates the source of phasing information: blue/orange = haplotagged by wf-human-variation, grey = clustered by Mahi-mahi.



Find out more about repeat expansion detection with Mahi-mahi:
nanoporetech.com/bioinformatics-tools



References

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