How Benthic Helped Sequence Bio Clarify HLA Risk Haplotypes in a Family-Based Multiple Sclerosis (MS) Study

Benthic Genomics partnered with Sequence Bio to generate phased, high-resolution HLA outputs from short-read whole genome sequencing data, helping the team further characterize and contextualize MS-risk haplotypes within a broader family-based analysis of multiple sclerosis in the founder population of Newfoundland and Labrador.

The Challenge

Sequence Bio was conducting family-based whole genome analysis to identify rare variants associated with multiple sclerosis, but the HLA/MHC region remained a major analytical gap.

While the team already knew of HLA risk associations relevant to MS, standard short-read workflows failed to resolve the phased haplotypes and broader variant context of the entire MHC region. They also recognized the functional limitations of some open-source tools. For a study trying to connect rare inherited variation with known common immune gene linkage, Sequence Bio needed outputs that could reliably resolve phased HLA haplotypes and broader MHC variation across a familial cohort. Mako, from Benthic, is designed to address exactly this type of MHC analysis challenge.

To move the study forward for interpretation across individuals and families, Sequence Bio needed:

- Reliable HLA calls from existing short-read WGS data
- Phased sequences and variants across the entire MHC
- A high-performing, modern, actively maintained solution that aligned with Sequence Bio's stringent privacy and security requirements

The Results

- Generated phased, four-field HLA allele calls from short-read whole genome data
- Identified a recurring, strongly suggestive signal involving a known MS-risk haplotype in the disease cohort
- Added a clearer view of common immune-region risk to the family-based rare variant analysis
- Gained confidence drawing biologically meaningful conclusions from the HLA region

"Using Mako, we attained a new threshold of confidence in our HLA risk haplotype calls. This complemented our family-based rare variant analysis and helped reveal the interplay of rare and common variants in MS genetic aetiology in our cohort."

-Tom Barber, Chief Scientific Officer at Sequence Bio

The Benthic Difference

Modern HLA/MHC analysis from standard NGS

Mako provided a practical way to recover phased MHC haplotypes and high-resolution HLA calls from the whole genome data they had already generated, by reconstructing phased MHC haplotypes and generating MHC-wide variant calls.

Resolution and phasing that changed the analysis

Four-field HLA resolution and locus wide variants were valuable, but the bigger advantage was phased output. That gave the team a way to examine HLA patterns across the familial dataset and recognize that a known MS risk haplotype was common in the disease cohort.

Support from a team that understood the problem

Sequence Bio chose Mako in part because they wanted to work with a team actively maintaining a modern solution that truly addressed the needs of the study.

Why Benthic Genomics

Benthic Genomics builds purpose-built solutions for the hardest regions of the genome to analyze, starting with the MHC. These are regions where standard workflows often break down: highly polymorphic, structurally complex, and biologically important, yet too often under-analyzed because the tools were not designed for the job.

That focus made Benthic a strong partner for Sequence Bio. Instead of relying on general-purpose tools not built for the complexity of the HLA/MHC region, Sequence Bio worked with a team focused on making these regions interpretable from standard sequencing data.

Next Steps

If your team is generating short-read sequencing data and knows the HLA/MHC region matters to your biology, Mako offers a practical way to add clarity with phased immune-region variant and allele calls directly from your data.

Benthic Genomics
High-confidence analysis for complex genomic regions
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