Illuminating the MHC “dark regions” in ALS: Project MinE and UMC Utrecht fine-map HLA associations with Angler Imputation

Building upon the landmark 2021 Nature Genetics study that identified 15 ALS risk loci across 29,612 patients, Benthic Genomics partnered with the Veldink Lab at UMC Utrecht to address a critical remaining challenge: fine-mapping the HLA region. Using Benthic Genomics’ Angler Imputation, this collaboration successfully resolved genetic associations in the MHC that even the most comprehensive GWAS methods couldn't fully characterize, advancing our understanding of ALS genetics.

The Challenge

Navigating Immunogenomic “Dark Regions”

The Project MinE consortium, one of the world's largest ALS research initiatives, faced a critical challenge in their genome-wide association studies (GWAS). Despite having access to over 10,000 whole genome sequences and 135,000+ array-based samples, researchers encountered significant gaps in the Major Histocompatibility Complex (MHC) region.

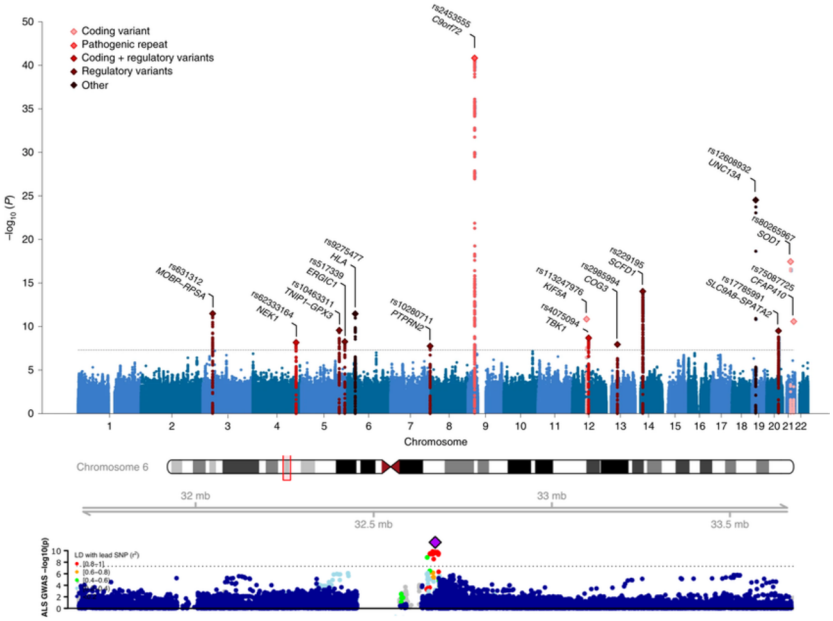


Figure 1. The initial 2021 GWAS study identified a significant ALS association within the HLA region, but a lack of data in the MHC's 'dark regions' prevented fine-mapping of the causal variant

Their GWAS study represented a monumental achievement in ALS genetics:

- Analyzed 29,612 ALS patients and 122,656 controls
- Identified 15 risk loci with distinct genetic architectures
- Revealed enrichment in glutamatergic neurons and autophagy pathways
- Established causal relationship with cholesterol levels

Despite employing state-of-the-art methods including SMR, eQTL, mQTL analyses, and rare variant burden testing, the study identified the HLA region as requiring tailored approaches for complete resolution. This represented an important opportunity for further investigation using specialized imputation methods for complex genomic regions.

The Solution

Advanced HLA Imputation with Superior coverage

Benthic Genomics collaborated with the original research team to apply their newly developed imputation technology, Angler, to address these challenges.

Key Technical Achievements

Dark Region Resolution	HLA Fine-Mapping	Massive Scale Processing
Benthic filled in missing variants in previously inaccessible delta-block regions in the MHC locus	Benthic progressed the analysis from regional association to specific HLA allele identification	Benthic processed >15,000 WGS samples and imputed variants for >135,000 array samples

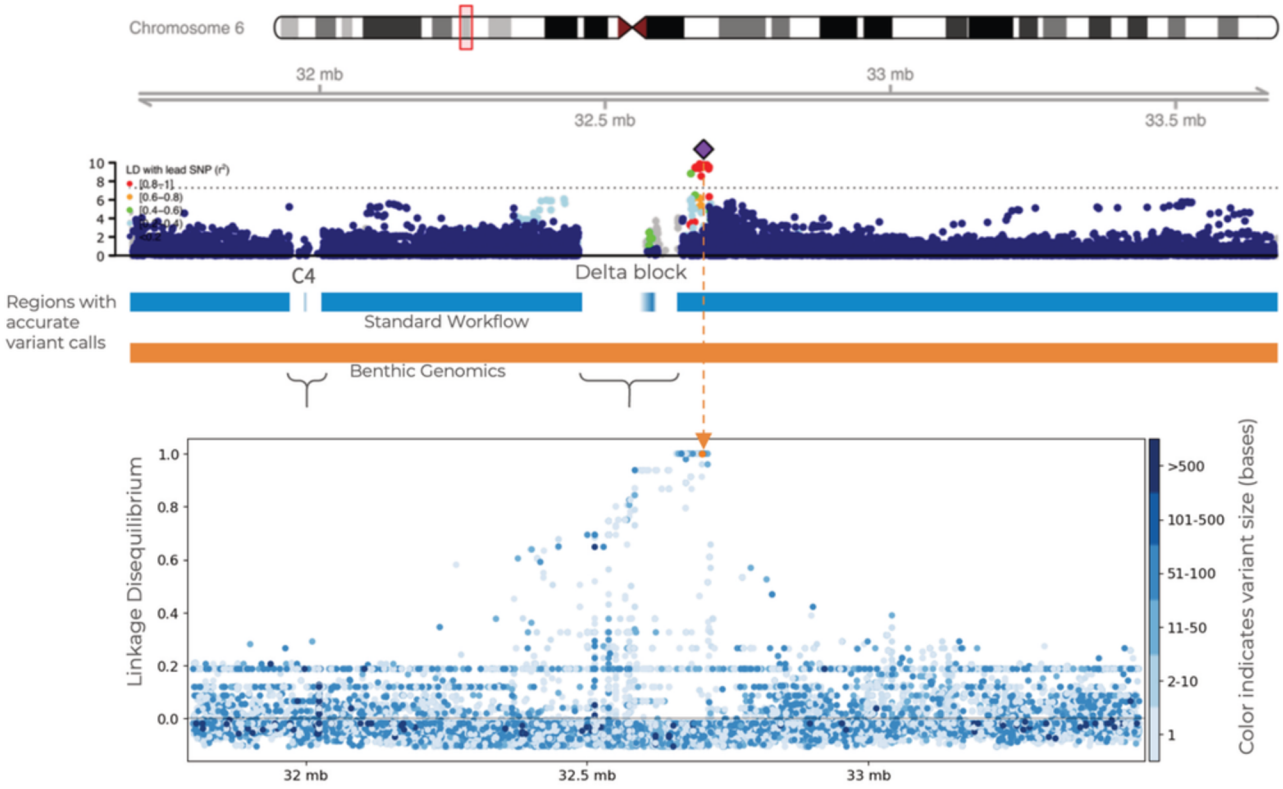


Figure 2. Benthic's Angler Imputation successfully resolved the 'dark regions' of the MHC, filling in previously missing variants to allow for a complete association analysis; Strong linkage disequilibrium suggests that the missing region is important

Implementation & Results

Working in close collaboration with the team at Project MinE, Benthic Genomics applied Angler Imputation to address the specific technical challenges of the MHC region – one of the most polymorphic and complex regions in the human genome.

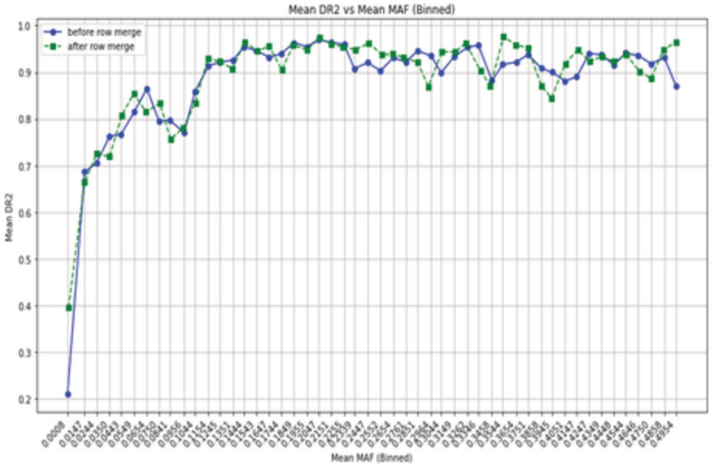


Figure 3. The imputation showed high accuracy with DR² values demonstrating strong correlation between imputed and actual genotypes. The mean DR² vs. Mean Minor Allele Frequency (MAF) analysis confirmed reliable imputation even for rare variants.

Key Findings

Identified three top association hits in the MHC region

Successfully associated SNPs with specific HLA-deltablock haplotypes, providing clearer interpretation of genetic associations

Meta-analysis across multiple strata revealed 51+ significant positions in previously unmapped "sequencing gap" areas

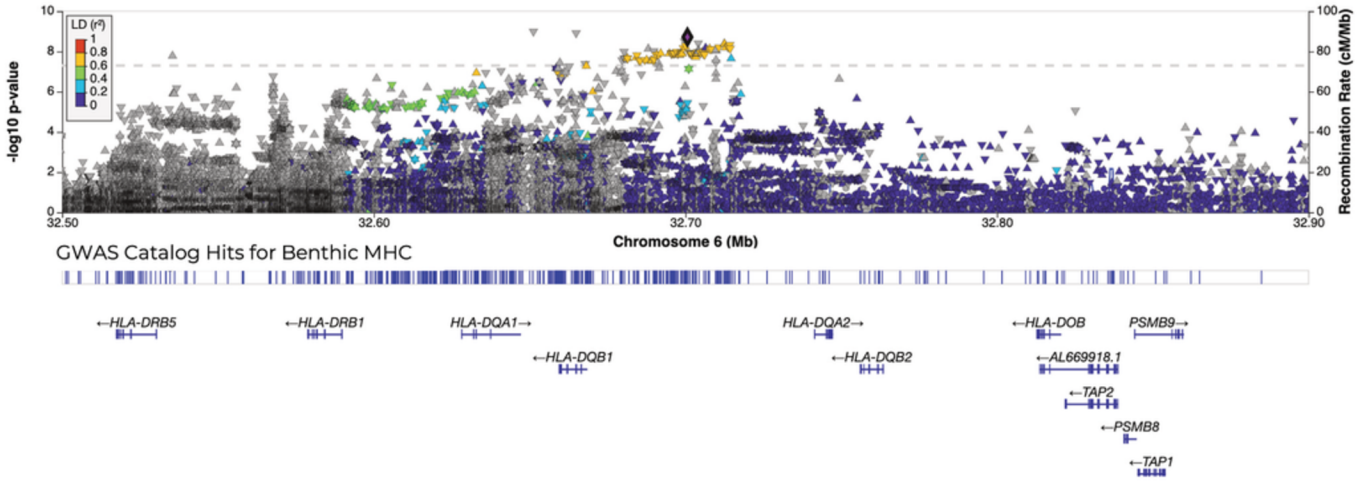


Figure 4. Showing linkage disequilibrium for one of three novel association signals for ALS that was identified using the newly imputed data, a discovery made possible by filling in the previous variant gap.

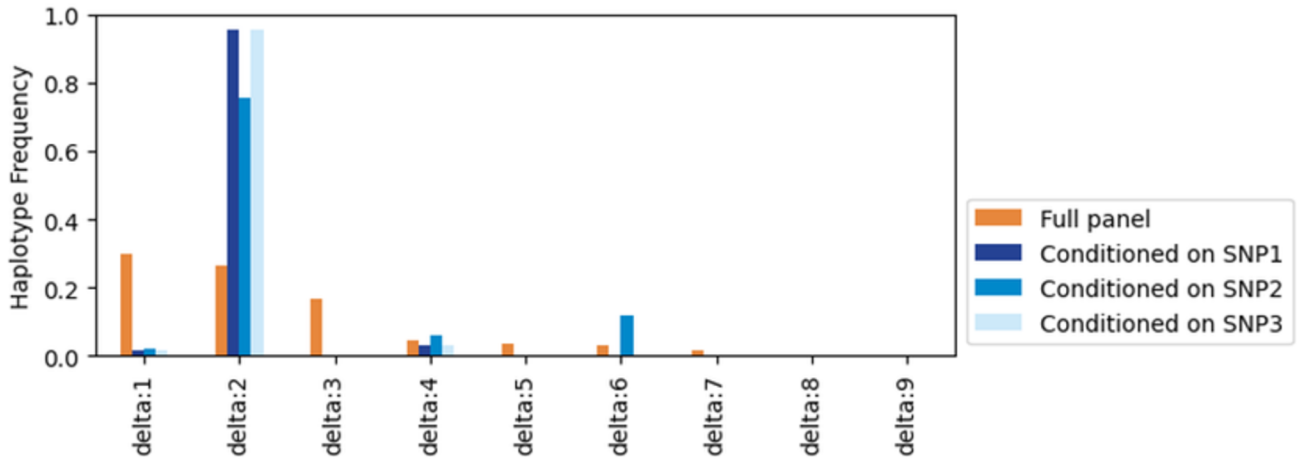


Figure 5. The analysis linked the top associated SNPs to specific HLA-deltablock haplotypes. Orange shows the frequencies of different HLA-deltablock haplotypes for the full panel, the blues show these frequencies when conditioning on the presence of one of the three top associated SNPs identified in the association study.

Why This Matters For Researchers

Large-scale studies like Project MinE generate an extraordinary foundation of statistical power, but their true impact depends on resolving the hardest-to-map regions of the genome. By combining a global dataset with specialized tools such as Angler Imputation, researchers can now extract insights that were previously inaccessible, and turning statistical associations into precise biological understanding.

Maximizing Research ROI

The 29,612-patient study provided statistical power; Angler ensured no genetic information was left unexplored in critical regions

Superior Coverage & Accuracy

Unlike traditional tools, Angler can impute variants in previously inaccessible genomic regions and maintain high accuracy

Scalability

By successfully processing more than 150,000 genomes and arrays, Angler proves it can scale alongside international consortia and biobank initiatives

Clinical Relevance

Researchers can apply Angler findings directly to candidate gene prioritization, functional follow-up studies, and translational pipelines

Conclusion: The Future of HLA Analysis

The successful fine-mapping of HLA associations in ALS demonstrates the power of combining large-scale GWAS with specialized regional analysis tools. By building upon the foundation of the Nature Genetics study, this collaboration shows how targeted technological solutions, like Angler Imputation, can resolve even the most challenging questions in genomics.

The landmark 2021 study mapped the genetic architecture of ALS with unprecedented scope, identifying 15 crucial risk loci. While the study found significant associations in the HLA region, the authors noted they 'could not prioritize a specific gene' within this locus despite the strong signal. Angler provided the specialized precision needed to convert these association signals into specific, identifiable HLA alleles and genes. For the MHC region, it's the difference between detecting a significant association and achieving the fine-mapping resolution needed to explore causal variants.

Dr. Jan Veldink, Analysis Program Director at Project MinE and senior author of the 2021 Nature Genetics study, recognized the unique value of this specialized approach:

"For Project MinE, I'd really like us to focus our efforts on this HLA approach. It feels like the most effective way forward."

Dr. Jan Veldink, Analysis Program Director at Project MinE

This exclusive commitment underscores the superior performance of Benthic's imputation technology compared to traditional methods, and its value for HLA research going forward.

About The Collaboration

This project represents an ongoing partnership between Benthic Genomics and the Veldink Lab at UMC Utrecht, with continued analysis and publication preparation underway.

About Benthic Genomics

Benthic Genomics converts complex genomic regions into crisp, actionable, and high-confidence genomic calls – at higher precision and scale compared to standard microarray and NGS methods.

Our software platform is compatible with a wide range of genomic input types – from microarray to short-read and even long-read sequencing – giving you high-resolution genotyping and variant calls across dozens of hard to characterize immune genes.

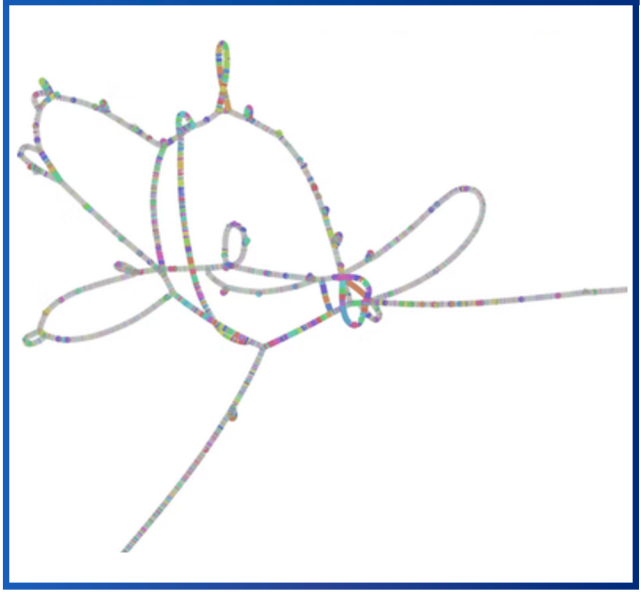
Advanced Graph-Based Algorithms

Our algorithms for assembly, alignment, imputation, and phasing are specifically designed to navigate the complexity captured in our reference graph – delivering superior analytics and highly accurate allele calling and interpretation.

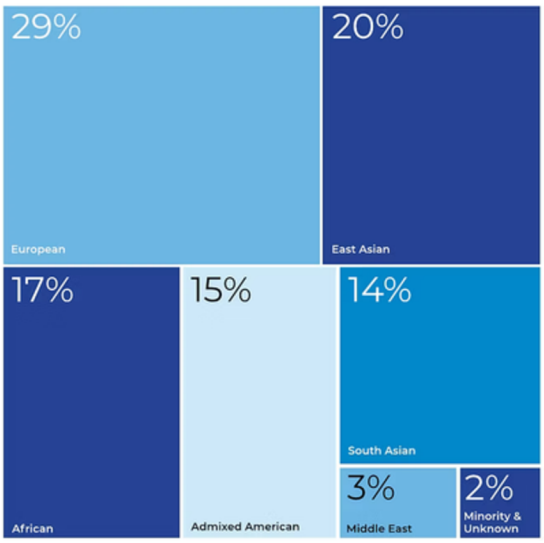
Unprecedented Diversity & Detail

Our graph-based pan-immune reference was developed using thousands of short-read samples and incorporating several hundred high-resolution, long-read phased haplotypes of the MHC, NKC, and LRC immune regions.

HLA Delta Block of just 9 individuals showcases complexity of the region



Superpopulation Representation in Angler™ Reference Panel



Take the Next Step in HLA Analysis

Whether you're advancing published findings or starting fresh analysis, Angler can help you fully characterize the MHC region

Explore Angler at **benthic.bio/angler**
Request a demo of Angler on your data at **benthic.bio/#demo**