The MHC Diversity in Africa Project (MDAP) Pilot - 125 African high resolution HLA types from 5 populations

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Why the MHC?

The major histocompatibility complex (MHC), or human leukocyte antigen (HLA) in humans, is a highly diverse gene family with a key role in immune response to disease; and has been implicated in auto-immune disease, cancer, infectious disease susceptibility, and vaccine response. It has clinical importance in the field of solid organ and bone marrow transplantation, where donors and recipient matching of HLA types is key to transplanted organ outcomes.

Better understanding of MHC diversity can provide important insights into population history and adaptive evolution; in addition to being a resource for medical genetics and allowing fine mapping of causitive variants from genome wide association studies.

Why Africa?

Reference databases [1] have historically been based largely upon samples taken European populations, and the full extent of diversity in Africa remains poorly understood. This presents a barrier to genetic studies, as it leaves us unable to fine map variation in the African MHC which relates to clinically significant variants, such as those involve in T2D or vaccine effectiveness. Here, we present the first systematic characterisation of HLA diversity within Africa using modern sequencing techniques in the pilot phase of the MHC Diversity in Africa Project. Towards this we assess third generation sequencing techniques in order to provide the first resource of high resolution HLA types across Africa.

Pilot Method

To validate our sequencing technique and test our analysis methods we recruited 125 samples evenly taken from 5 populations. DNA was extracted and sequenced three ways: Sanger SBT, Illumina HiSeq X WGS and amplicon sequencing with the PacBio RS II.

Pilot Results

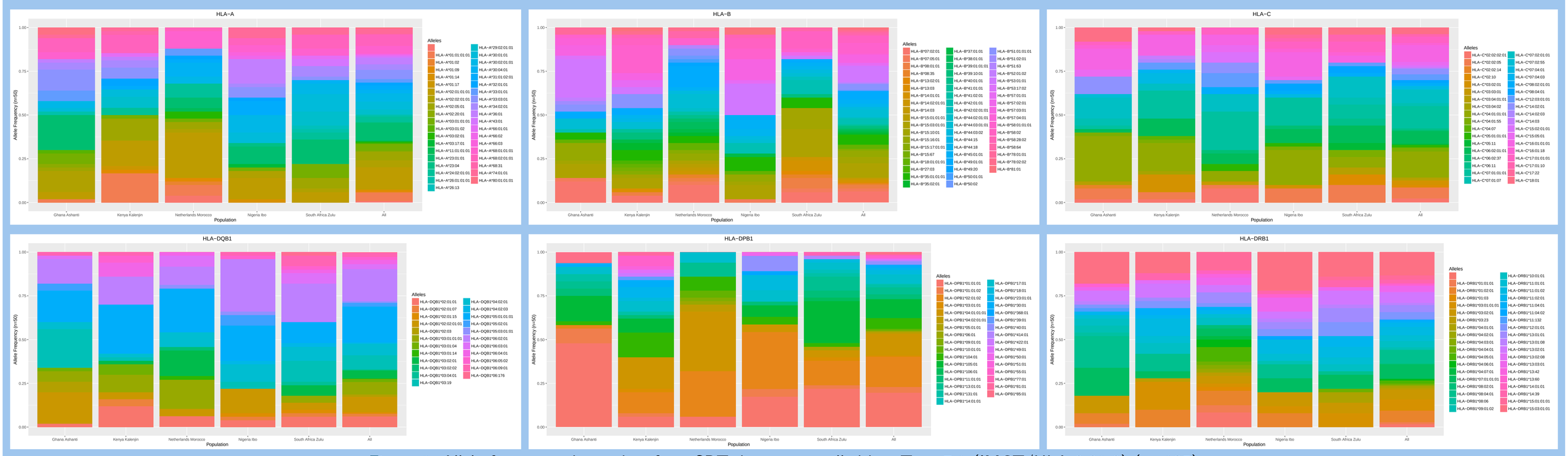

Figure 1: Allele frequency data taken from SBT data types called by uType 7.1 (IMGT/HLA 3.21.0) (n=125)

MDAP Project Summary

Having validated our sequencing methods, we have proposed to sequence and type 5,000 samples from more than 50 populations across Africa. To provide broader information about the variation across the MHC we will be performing additional long read sequencing to generate platinum quality assemblies for a subset of 50 samples.

Conclusion

Our initial results from this pilot study reflected the diversity we hypothesised to exist: that each of populations each had a large number of distinct alleles; the existence of new novel variants and differing modal alleles for each population. By continuing to increase our reference panel size we can capture this diversity and increase our power to make discoveries.

References

[1] James Robinson, Jason A. Halliwell, James D. Hayhurst, Paul Flicek, Peter Parham, and Steven G. E. Marsh.
The IPD and IMGT/HLA database: allele variant databases.
Nucleic Acids Research, 43(D1):D423–D431, 2015.

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Igbo & Kalenjin - Charles Rotimi, National Human Genome Research Institute, National Institute of Health (NIH), Bethesda, USA
Moroccans - Charles Agyemang, Dep of Public Health, Academisch Medisch Centrum (AMC), Amsterdam, The Netherlands
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