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DataSheet

Axiom™ HLA Analysis

Automated, high-resolution HLA typing from genotyping data

Highlights

- Coverage of 11 major histocompatibility complex (MHC) Class I and Class II loci
- Class I loci: HLA-A, -B, -C
- Class II loci: HLA-DQA1, -DQB1, -DPA1, -DPB1, -DRB1, -DRB3, -DRB4, -DRB5
- 2- and 4-digit resolution
- Compatible with any genotyping platform

Applications

- Genome-wide association studies
- Targeted genotyping studies
- Patient stratification for clinical trials
- Transplant research
- Transplant immunology and immunogenetics
- Transplantation donor/recipient screening

Axiom™ HLA Analysis utilizes a unique imputation algorithm developed by leaders in the field of statistical genetics to enable the inclusion of HLA typing in genome-wide association studies without requiring additional testing.

The human leukocyte antigen (HLA) complex has long been established as a highly variable region in the human genome.[1,2] This gene complex encodes for proteins of fundamental importance in immune function. The rich genetic diversity in this region has been associated with disease susceptibility (e.g., autoimmune[3] and inflammatory[4] diseases, as well as communicable and infectious[5] diseases), drug metabolism,[6] transplant medicine,[7] and many other genetic conditions. The largest number of replicated associations in the human genome reside in the HLA region;[8] however, this portion of chromosome 6 (with over 13,000 alleles identified[9]) is often overlooked due to the complex genetics of this region.[1]

Imputation and HLA typing

Imputation is a valuable tool used to infer missing single-nucleotide polymorphism (SNP) genotype data from genome-wide association studies because it increases the power of these studies to reveal more SNPs that can be evaluated for associations.[10] With advanced imputation techniques, it is now possible to gain insights into the hyper-variable and genetically relevant HLA region of the genome to identify possible associations between HLA types and disease. The extreme density of linked SNPs and long-distance linkage disequilibrium (LD) relationships in the HLA region[3] enable the imputation of HLA alleles from genotypes across the extended MHC region.

A unique haplotype graph is created for each HLA locus, which represents all possible haplotypes and HLA alleles present in the reference panel, allowing for the same HLA type to be accessed via multiple paths in the graph.[11] The genotypes of each individual are compared to the haplotypes present in the graph file to determine the precise HLA allele present in the individual. Using a multi-population reference graph to create haplotype maps,[11] Axiom HLA Analysis is able to impute HLA types for 11 major Class I and Class II loci to sub-type (4-digit) resolution for mixed populations. The current reference panel is heavily weighted for Caucasian populations and, as such, higher imputation accuracies and call rates may be observed in Caucasian populations.

Axiom HLA Analysis software

The software package can be installed and used to analyze genotyping data from Axiom® genotyping arrays and Genome-Wide Human SNP Array 6.0 from Affymetrix. Performance on each array type is directly related to the degree of coverage in the extended MHC region in each data set as well as the representation of specific populations and rare alleles in the reference panel.

System requirements

Microsoft Windows® 7 Professional SP1	
Operating system (bits)	64-bit
Processor (CPU)	2.83 GHz Intel® Pentium® Quad Core
Memory (RAM)	8 GB RAM (minimum) 16 GB RAM (recommended)
Quality recommendations	Genotyping data should meet platform specifications for performance

*Software can be downloaded for analysis of genotyping data sets from Affymetrix. Please inquire for analysis services of data sets from other platforms.

Affymetrix Research Services Laboratory (ARSL) HLA typing services

Genotyping data from platforms other than those from Affymetrix can be submitted to ARSL for HLA typing. Any high-quality genotyping data set with sufficient coverage of SNPs in the extended MHC can be analyzed for HLA types.

Results

The ability to determine HLA types from new and existing genotyping data in parallel with genome-wide and targeted genetic analyses will enable new scientific insights with greater efficiency. For genotyping data sets generated with products from Affymetrix with adequate coverage in the extended MHC region, an average 4-digit imputation accuracy of 97% and 97% call rate on diverse European panels is expected.

Data submission requirements for HLA analysis by ARSL

Genotype data in variant call format (.vcf)	
.vcf columns required	Chromosome# (#CHROM), Position (POS), RSID (ID), Reference allele (REF), Alternate allele (ALT), Genotype (GT)
Batch size	≥20 samples
SNP count	≥1,500*
Quality recommendations	Genotyping data should meet platform specifications for performance

*SNP count is the minimum number of SNPs in the extended MHC region.

Results from Axiom™ HLA Analysis. Validation results using Axiom™ HLA Analysis with a posterior probability threshold of 0.7. #Concordant alleles, and concordance rates are based on comparison to the International Histocompatibility Working Group (IHWG)-reported HLA types for each allele; concordance, and call rate are used as measures of accuracy on a per-locus level.

Locus	Over-all	HLA-A	HLA-B	HLA-C	HLA-DPA1	HLA-DPB1	HLA-DQA1	HLA-DQB1	HLA-DRB1	HLA-DRB3	HLA-DRB4	HLA-DRB5
#Alleles	2,469	296	294	288	288	294	292	240	286	65	59	19
#Concordant alleles	2,394	292	285	279	284	282	287	238	282	58	28	19
Concordance	97.0	98.6	96.9	96.9	98.6	95.9	98.3	99.2	98.6	89.2	98.3	100
Call rate	98.8	100	99.7	98.3	99.7	99.3	99.7	99.2	96.6	100	98.3	100

References

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2. Mungall A. J., *et al.* The DNA sequence and analysis of human chromosome 6. *Nature* **425**(6960):805–811 (2003).
3. Gough S. C., *et al.* The HLA region and autoimmune disease: associations and mechanisms of action. *Current Genomics* **8**(7):453–465 (2007).
4. Heap G. A., *et al.* The genetics of chronic inflammatory diseases. *Human Molecular Genetics* **18**(R1):R101–R106 (2009).
5. Blackwell J. M., *et al.* HLA and infectious diseases. *Clinical Microbiology Reviews* **22**(2):370–385 (2009).
6. Pompeu Y. A., *et al.* The structural basis of HLA-associated drug hypersensitivity syndromes. *Immunological Reviews* **250**(1):158–166 (2012).
7. Chinen J., *et al.* Transplantation immunology: solid organ and bone marrow. *Journal of Allergy and Clinical Immunology* **125**(2 Suppl 2):S324–S335 (2010).
8. de Bakker P. I., *et al*. Interrogating the major histocompatibility complex with high-throughput genomics. *Human Molecular Genetics* **21**(R1):R29–36 (2012).
9. From IPD – IMGT/HLA database statistics, http://www.ebi.ac.uk/ipd/imgt/hla/stats.html, accessed on September 8, 2015.
10. Marchini J., *et al.* Genotype imputation for genome-wide association studies. *Nature Reviews Genetics* **11**(7):499–511 (2010).
11. Dilthey A., *et al.* Multi-population classical HLA type imputation. *PLoS Computational Biology* **9**(2):e1002877 (2013).

Ordering information

Part number	Product	Description
600741	Axiom™ HLA Analysis	HLA typing from genotype data from Affymetrix (compatible with Axiom® genotyping arrays and Genome-Wide Human SNP Array 6.0)
000911	HLA Typing Analysis Services	Affymetrix Research Services Laboratory (ARSL) data analysis option for analysis of genotyping data (compatible with genotyping data generated by products from Affymetrix and other platforms)
000912	Axiom™ HLA Analysis Services 96	ARSL HLA typing analysis available for add-on to any service assay order for 96-format Axiom® genotyping arrays
000913	Axiom™ HLA Analysis Services 384	ARSL HLA typing analysis available for add-on to any service assay order for 384-format Axiom® genotyping arrays

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