Axiom® Transplant Genotyping Array

Content summary

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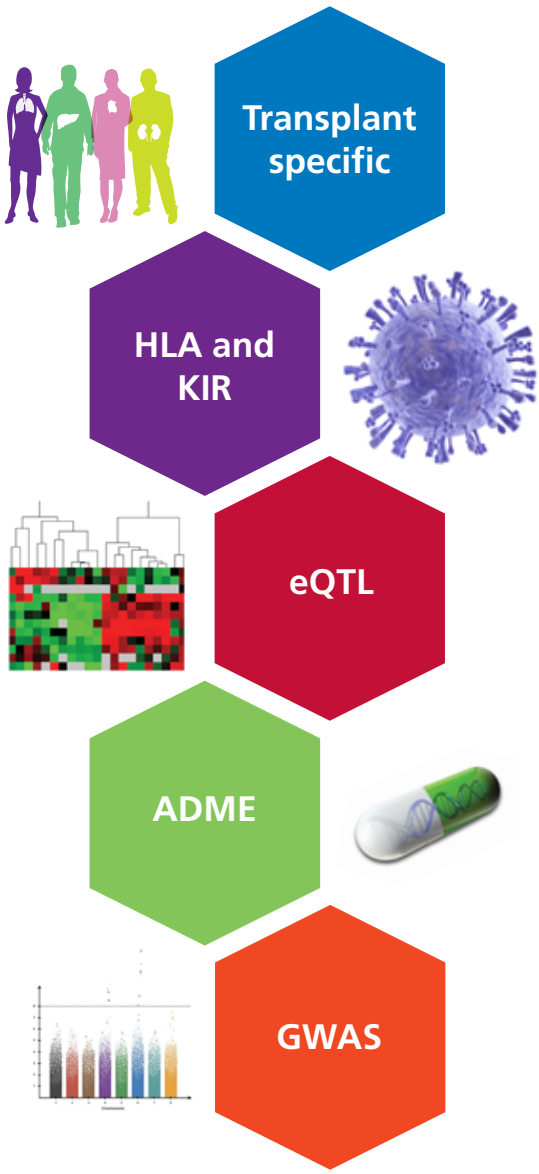
Axiom® Transplant Genotyping Array was designed with the International Genetics & Translational Research in Transplantation Network (iGeneTRAiN), a network established to further research in the area of solid-organ transplantation (specifically: heart, kidney, liver, and lung transplants) by utilizing genetic information to improve transplant success and tailoring treatments for patient-specific recommended therapeutics. iGeneTRAiN's ultimate goal is to translate this information into clinical practice and to minimize graft rejection and complications of rejection.



The design was based on the latest genome-wide association study (GWAS) arrays with customization specific to transplantation research. A GWAS framework was built from UK Biobank Axiom® Array and Axiom® Biobank Genotyping Array to facilitate collaboration and empower meta-analyses.

This document provides an overview of the content of Axiom® Transplant Genotyping Array, which was designed by the iGeneTRAiN Array Design Group. (Membership of the design group is listed at the end of this document.) There are 782,000 single nucleotide polymorphisms (SNPs), copy number variants (CNVs), and insertion/deletion (indel) markers on this array.

Further details are included in Table 1. At the highest level, the general array design philosophy was to

- Design a genome-wide SNP array to be used to identify genetic variation in loci of significant importance in transplantation.
- Provide a comprehensive genome-wide imputation grid for major populations, including those of European, Asian, and African ancestry.
- Include content specific for transplantation research, including functional variants, loss-of-function markers, and CNVs.

Table 1: Axiom® Transplant Genotyping Array content summary.

Category/Markers of specific interest	Number of markers
Module content from UK Biobank Axiom® Array	
Human leukocyte antigen (HLA) and killer immunoglobulin-like receptor (KIR)	8,894
Phenotype associations	8,136
Known CNVs	2,369
Expression quantitative trait loci (eQTL)	17,115
Lung tissue/pulmonary function	8,645
Expanded major histocompatibility complex (MHC) and KIR content	
Multi-ethnic HLA haplotype tagging	421
Type 1 Diabetes Genetic Consortium (T1DGC) HLA imputation panel	4,794
Non-redundant MHC-validated SNPs	13,732
Transplant-specific content	
Pharmacogenomic	9,500
Candidate genes	23,800
Functional variants	
Exonic/coding variants	168,000
Loss of function	28,128
Untranslated region (UTR)	184,000
A priori associations	8,136
CNVs/copy number polymorphisms	27,370
Genome-wide coverage	
Genome-wide imputation grid	296,000
Genome-wide coverage for non-European populations	50,000
Genome-wide booster	135,000
Compatibility markers	18,000
Total number of markers	782,000

The following provides detailed descriptions of the specific categories of content. The number of markers in each category refers to the number of markers on the array that were selected from a given category. A marker can be selected for more than one category but appears only once on the array.

Category/Markers of specific interest

1. Module content from UK Biobank Axiom Array

These markers were chosen from UK Biobank Axiom Array to allow cross-platform and cross-cohort meta-data analysis.

1.1. HLA (7,348 markers) and KIR (1,546 markers)
Genes in the HLA region (chr6) and KIR region (chr19) are known to be important in immune response but are difficult to directly assay on commercial arrays. Markers have been added to the array to facilitate imputation of these alleles.

1.2. Phenotype associations (8,136 markers)
Content was selected from markers in the National Human Genome Research Institute (NHGRI) *A Catalog of Published Genome-Wide Association Studies* (up to mid 2013).

1.3. Known CNVs (2,369 markers)
A set of known CNVs was selected to cover CNV regions and evaluate for genomic structural elements. Markers were added to ensure dense coverage within known CNV regions; assays were included for known breakpoints, where possible.

1.4. eQTL (17,115 markers)
eQTL markers were included to support the mapping of functional non-coding variations to identify genetic markers associated with gene transcription variability and differential gene expression.

1.5. Lung tissue/pulmonary function (8,645 markers)
A set of markers with established or putative association with lung function, lung disease, smoking behavior, or any combination of these, was included on the array.

2. Expanded MHC and KIR content

These markers were chosen in addition to the HLA module listed above in order to improve imputation of major HapMap populations, including African, Asian, and European populations.

2.1. Multi-ethnic HLA haplotype tagging SNPs (421 markers)
SNPs that are in linkage disequilibrium (LD) with HLA alleles were included for improved imputation of HLA alleles in multi-ethnic populations.

2.2. T1DGC HLA imputation panel (4,794 markers)
A set of markers from the T1DGC was chosen for direct tiling, tagging, or both by LD for HLA imputation.

2.3. Non-redundant MHC SNPs (13,732 markers)
Validated, non-redundant MHC SNPs were selected from existing genotyping platforms, including Infinium® MetaboChip and ImmunoChip.

3. Transplant-specific content

This content module is customized for metabolic and pharmacogenomic markers that are known and potentially relevant in transplantation.

3.1. Pharmacogenomic (9,500 markers)
Absorption, distribution, metabolism, and excretion (ADME) markers were selected with known relevance to, or involvement in, the metabolism of immunosuppression therapeutics and other transplant-related therapeutics.

3.2. Deeper coverage of transplant candidate genes (23,800 markers)
SNPs related to transplant outcome, transplant associations, and response to transplant prescription therapies were selected to maximize coverage across major populations.

4. Functional variants

Markers of putative coding and non-coding loss-of-function variants were selected from whole-exome sequencing reference datasets.

4.1. Exonic and coding (168,000 markers)
Markers were selected from Axiom Biobank Genotyping Array, including putative exonic or coding single-nucleotide variants.

4.2. Loss of function (28,128 markers)
Markers were selected from Axiom Biobank Genotyping Array as well as human disease mutation and exome databases.

4.3. UTR (184,000 markers)
Markers were chosen to capture variants that affect functional gene expression.

4.4. *A priori* associations (8,136 markers)
Variants were selected based on calculated genome-wide significance as reported in NHGRI GWAS catalog.

4.5. CNVs and copy number polymorphisms (27,370 markers)
Variations in copy number cover 2,200 curated CNV regions.

5. Genome-wide coverage

Markers were selected for genome-wide association of major populations as defined by the HapMap project (http://hapmap.ncbi.nlm.nih.gov/). These include individuals of African, Asian, and European descent.

5.1. Genome-wide imputation grid (296,000 markers)
Markers were selected to provide genome-wide coverage in Caucasian European populations of common markers.

5.2. Genome-wide coverage for non-European populations (50,000 markers)
Additional markers were selected from Axiom Biobank Genotyping Array for improved coverage of non-European populations, including individuals of African and Asian descent.

5.3. Genome-wide booster panel (135,000 markers)
Additional GWAS markers were included to improve imputation coverage specifically for African and European populations.

5.4. Compatibility markers (18,000 markers)
Markers were included to optimize and standardize genotyping quality control.

Tagging strategy

Markers of high interest for inclusion on the array were first checked for their presence in Axiom® Genomic Database, which contains markers that have been experimentally validated for successful genotyping with Axiom® Genotyping Solution. Markers that had been validated were selected for inclusion on the array. Markers that had not been previously validated were checked for the existence of a good tag in the validated set of markers, and if one existed, were selected as the best such tag for inclusion on the array.

Membership of iGeneTRAiN and the Axiom® Transplant Genotyping Array Design Group

- **Yun R. Li**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **Jessica van Setten**, University Medical Center Utrecht
- **Shefali S. Verma**, Center for Systems Genomics
- **Michael V. Holmes**, Penn Transplant Institute
- **Hui Gao**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **Monkol Lek**, Massachusetts General Hospital, Broad Institute of Harvard and MIT
- **Nikhil Nair**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **Hareesh Chandrupatla**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **Baoli Chang**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **Konrad J. Karczewski**, Massachusetts General Hospital, Broad Institute of Harvard and MIT
- **Chanel Wong**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **Maede Mohebnasab**, The Children's Hospital of Philadelphia
- **Laura Steel**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **Takesha Lee**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **James Garifallou**, The Children's Hospital of Philadelphia
- **Hongzhi Cao**, BGI-Shenzhen, University of Copenhagen
- **Weihua Guan**, University of Minnesota
- **Aubree Himes**, The Children's Hospital of Philadelphia, Penn Transplant Institute
- **Jacob van Houten**, The Children's Hospital of Philadelphia
- **Andrew Pasquier**, The Children's Hospital of Philadelphia
- **Reina Yu**, The Children's Hospital of Philadelphia
- **Elena Carrigan**, The Children's Hospital of Philadelphia
- **Baolin Wu**, University of Minnesota
- **Amein K. Al-Ali**, University of Dammam
- **Hakon Hakonarson**, The Children's Hospital of Philadelphia
- **Teresa Webster**, Affymetrix, Incorporated
- **Suganthi Balasubramanian**, Yale University
- **Matthew B. Lanktree**, Penn Transplant Institute
- **William S. Oetting**, University of Minnesota
- **Pamala A. Jacobson**, University of Minnesota
- **Marylyn D. Ritchie**, Center for Systems Genomics
- **Ajay K. Israni**, Hennepin County Medical Center
- **Abraham Shaked**, Penn Transplant Institute
- **Folkert W. Asselbergs**, University Medical Center Utrecht, University College London, ICIN Netherlands Heart Institute
- **Daniel G. MacArthur**, Massachusetts General Hospital, Broad Institute of Harvard and MIT
- **Yontao Lu**, Affymetrix, Incorporated
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Axiom Transplant Genotyping Array is **For Research Use Only. Not for use in diagnostic procedures.**

Affymetrix, Inc: (US) +1-888-362-2447, +1-408-731-5000 ■ **(EU)** +44-(0)1628-552550 ■ **(JP)** +81-(0)3-6430-4020 ■ **(CN)** +86-21-63915511
eBioscience Products: (US) +1-888-999-1371, +1-858-642-2058 ■ **(EU)** +43 1 796 40 40 305 ■ **(JP)** +81-(0)3-6430-4020
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