Axiom Precision Medicine Research Array

Driving deeper scientific insights and understanding of individual genetic diversity in global precision medicine screening research

Accelerating the promise of precision medicine cohort studies requires a cost-effective, broad-population screening platform with proven clinical research utility. This requires a genotyping solution that offers dense genotyping, delivers reproducible results, and helps ensure that all markers are accessible in every batch. The Applied Biosystems™ Axiom™ Precision Medicine Research Array (PMRA) delivers these features, which are vital to the translation of research results into clinical research insight and to the future wide-scale adoption of precision medicine.

Highlights

- Powered by the Applied Biosystems™ Axiom™ Genotyping Solution and used by biobanks worldwide, the Axiom PMRA offers a genome-wide imputation grid from Phase III of the 1000 Genomes Project and from the NHGRI-EBI GWAS catalog published as of May 2016, offering the most up-to date content, broad coverage, and high accuracy for disease association studies across populations [1–3]
- Includes carefully selected, clinically significant pathogenic variants including those implicated for actionable genetic risk across a wide range of populations
- Covers common variants associated with cancer identified by GWAS per the NHGRI-EBI
- Includes immune- and transplant-related variants including human leukocyte antigen (HLA) markers analyzed with corresponding Applied Biosystems™ Axiom™ HLA Analysis Software and killer-cell immunoglobulin-like receptors (KIR) to facilitate deeper understanding of rejection risks and causes in transplant-related research studies [4]
- Covers blood phenotype markers chosen from GWAS and candidate gene studies for their association with red blood cell groups, the regulation of formation of red blood cells and platelets, and the regulation of blood homeostasis
- Includes SNPs used as fingerprint SNPs by the University of Washington as well as the Broad Institute of MIT and Harvard; these markers are shared among several major genotyping platforms to facilitate sample tracking

The Axiom PMRA was designed specifically for use by scientists in basic and clinical research labs, research institutions, and direct-to-consumer genomic organizations. The Axiom PMRA helps to better understand the interplay between human genetics and the susceptibility to complex diseases, and to translate that understanding to potential future clinical use.

Table 1. Axiom PMRA key marker groups.

Variant category	Number of markers*
Genome-wide imputation grid	>800,000
NHGRI-EBI GWAS catalog	>15,000
ClinVar	>23,000
American College of Medical Genetics (ACMG, subset of ClinVar)	>9,000
Additional high-value markers (subset of ClinVar: *APOE*, *BRCA1/2*, *DMD*, *CFTR*)	>2,000
HLA	>9,000
KIR	>1,400
Autoimmune/inflammatory	>250
Pharmacogenomic	>1,200
Blood phenotype	>2,000
Common cancer variants	>300
Loss of function	>33,000
Expression quantitative trait loci (eQTL)	>16,000
Fingerprinting and sample tracking	>300
Total markers	**902,527**

* Content in categories may overlap.

Variants covering diseases and human health conditions

The Axiom PMRA includes several thousand novel risk variants that have been implicated in human diseases and conditions. The array includes pathogenic variants selected from ClinVar, including APOE markers associated with Alzheimer's disease [5,6]. Until now, such markers were unavailable on any microarray product. Table 2 shows the number of markers that fall into various categories per the OMIM™ and ClinVar databases.

Cancer risk variants—The array covers over 17,000 cancer risk variants from the NHGRI-EBI GWAS catalog, various publications, and the OMIM database. This includes variants associated with risks for colorectal [7], prostate [8], ovarian [9], lung [10], and breast cancers.

Mental health, behavioral, and neurodevelopmental conditions variants—This group covers over 19,000 variants, of which a subset is associated with neuroticism as identified by the Applied Biosystems™ UK Biobank Axiom™ Array [11,12].

Immune-related variants (including autoimmune and inflammatory variants)—The array covers over 200 variants that were included on the UK Biobank Axiom Array and show evidence for association with specific autoimmune and inflammatory disorders, including ulcerative colitis, Crohn's disease, type 1 diabetes, Graves' disease, Hashimoto's thyroiditis, and celiac disease. The array also includes novel variants that have been implicated in narcolepsy [13] and have been evaluated in transplant studies [4].

Loss-of-function (LoF) variants—Markers are included to detect genetic changes that are predicted to completely disrupt the function of protein-coding genes, including rare and likely deleterious LoF alleles, predicted severe disease-causing variants, and common LoF variants in nonessential genes. The array includes over 1,000 autosomal recessive and over 500 autosomal dominant predictive variants.

Cardiovascular disease variants—These variants cover most common diseases in cardiology, including hypertension, atrial fibrillation, coronary heart disease, familial hypercholesterolemia, familial hypertrophic cardiomyopathy, Marfan syndrome, and congenital long QT syndrome.

Table 2. Markers classified into disease research categories and important subcategories according to OMIM and ClinVar databases.

Categories/subcategories	No. of markers
Cancer risk variants	>17,000
Myeloma risk variants	12
Lung cancer risk variants	642
Breast cancer risk variants	931
Ovarian cancer risk variants	281
Gastric cancer risk variants	1,466
Leukemia risk variants	7,759
Colorectal cancer risk variants	5,669
Mental, behavioral, and neurodevelopmental risk variants	>19,000
Alzheimer's disease–associated risk variants	413
Parkinson's disease–associated risk variants	1,272
Schizophrenia-associated risk variants	526
Autism-associated risk variants	92
Autoimmune and inflammatory disease risk variants	>200
Celiac disease risk variants	88
Crohn's disease risk variants	34
Graves' disease risk variants	28
Clinical variants	>44,000
Pathogenic	36,111
Likely pathogenic	6,983
Loss-of-function variants	>33,000
Autosomal recessive	1,000
Autosomal dominant	502
Mitochondrial	117
Pathogenic or likely pathogenic	1,268
Congenital conditions	782
Novel/newly discovered variants not reported in dbSNP	15,343
Cardiovascular disease risk variants	>15,500
Variants for factors influencing health status	>2,000
Smoking and addiction risk variants	106
Alcohol dependence risk variants	30
Coffee consumption risk variants	18
Alcohol sensitivity risk variants	16
Allergy risk variants	121
Skin, hair, or eye pigmentation	1,519
Pharmacogenomic coverage	>1,600
Phase I enzymes	57
Phase II enzymes	51
Phase III enzymes/transporters	49
Respiratory disease risk variants	>700
Musculoskeletal disease risk variants	>8,000
Glaucoma risk variants	>300
Diabetes risk variants	>2,000
Obesity risk variants	>1,400

High imputation coverage and accuracy

The Axiom PMRA GWAS markers are common variants intelligently selected via a proprietary imputation-based marker selection strategy for genome-wide coverage in five major populations. These populations include African (AFR), European (EUR), Ad Mixed American (AMR), East Asian (EAS), and South Asian (SAS), as defined by the 1000 Genomes Project. Table 3 provides the number of imputed markers available on the Axiom PMRA for the five ancestral populations; Table 4 provides the imputation accuracy for GWAS markers with minor allele frequencies (MAF) >1% and >5%.

Table 3. Number of imputed markers with $r^2 > 0.8$ and MAF >1%.

Population	>1% MAF
AFR	14.5 M
EUR	8.6 M
AMR	10.0 M
EAS	7.4 M
SAS	8.5 M

Table 4. Imputation accuracy (mean r^2) calculated across all chromosomes.

Population	>1% MAF	>5% MAF
AFR	0.90	0.93
EUR	0.92	0.95
AMR	0.92	0.95
EAS	0.90	0.94
SAS	0.89	0.94

Precision medicine research and continuity of studies

Precision medicine research studies involving large cohorts are typically conducted over several years. Such studies interrogate clinical markers implicated in various diseases, pharmacogenomic markers, and immune-related markers, providing deeper insights into these important diseases and conditions. These long-term studies require a platform that can offer multiyear availability of 100% of the specific array content. Unlike bead-based technologies that may experience batch-to-batch variability and SNP dropouts with each manufacturing batch, the manufacturing technology used with Axiom arrays offers 100% fidelity and helps ensure all markers are present on every manufacturing batch for as long as necessary.

Array processing

Axiom genotyping solutions provide lot-to-lot reproducibility and utilize the powerful 96-sample format. The Applied Biosystems™ GeneTitan™ Multi-Channel (MC) Instrument automates array processing from target hybridization to data generation and can process up to eight array plates per week. Applied Biosystems™ Genotyping Console™ Software automates data analysis and includes allele-calling algorithms and user-friendly visualization tools.

The assay and workflow are fully automated and offer reduced hands-on time compared to comparable genotyping platforms, allowing the processing of more samples for a more comprehensive study.

Specifications

The Axiom PMRA meets the demands of multiyear precision medicine cohort studies, providing high-density genotyping arrays that enable reproducible results and no loss of SNP markers from lot to lot. Genotyping performance has been evaluated on 288 samples, including samples from the International HapMap Project, using stringent quality control metrics that cover average sample call rate, sample concordance, and reproducibility (Table 5).

Analysis workflow for the Axiom PMRA

The Axiom analysis workflow as described in the Axiom Genotyping Solution Data Analysis Guide (P/N 702961) is an advanced analysis technique that enables high flexibility in finding the most informative content for each study.

Table 5. Performance of the Axiom Precision Medicine Research Array.

Metric	Specification	Performance
Number of samples	–	288
Sample pass rate	≥95%	97.9%
Average call rate	≥95%	99.7%
Reproducibility	≥99.8%	99.95%
Average HapMap concordance	≥99.5%	99.8%

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References

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Ordering information

Product	Description	Cat. No.
Axiom Precision Medicine Research Array	Contains one 96-array plate; reagents and GeneTitan Multi-Channel Instrument consumables sold separately	902981
Axiom GeneTitan Consumables Kit	Contains all GeneTitan Multi-Channel Instrument consumables required to process one Axiom array plate	901606
Axiom 2.0 Reagent Kit	Includes all reagents (except isopropanol) for processing 96 DNA samples	901758

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