Axiom Precision Medicine Diversity Research Array

Driving deeper scientific insights into genetic factors relevant to disease research, genetic testing, and more

Key features

- >850,000 single-nucleotide polymorphisms (SNPs), insertions or deletions (indels), and copy number variations (CNVs) with dense whole-genome coverage
- >800,000 markers from phase III of the 1000 Genomes Project in the genome-wide imputation grid, selected using an imputation-aware design (Figure 1 and Table 1)
- >15,000 relevant variants covering the 59 genes recommended by the American College of Medical Genetics (ACMG59) associated with potentially severe health conditions such as familial hypercholesterolemia, breast cancer, and rare genetic disorders of enzyme deficiency
- >5,000 pharmacogenomic (PGx) research markers in >1,100 genes, offering comprehensive coverage of core and extended ADME genes across categories 1–4 established by the Pharmacogenomics Knowledgebase (PharmGKB)
- Star allele report and coverage of genes with known relevance to drug metabolism, including *CYP1A2*, *CYP2D6*, *CYP2B6*, *CYP2A6*, *SULT1A1*, *CYP2C19*, and *CYP2C8* when used with the Applied Biosystems™ Axiom™ 2.0 Plus Assay
- >16,000 relevant markers from the NHGRI-EBI Genome-Wide Association Studies (GWAS) Catalog, offering the most up-to-date content, broad coverage, and high accuracy for disease association studies [1-3]
- >1,100 markers for assessing common and rare blood types for applications in research on blood conditions such as bleeding disorders, sickle cell disease, and thalassemia
- >2,000 markers for genetic testing, including Y chromosome and mitochondrial markers for deep ancestry analysis and markers for lifestyle- and environment-associated conditions, most notably asthma, allergies, alcohol and smoking addiction, skin conditions, and obesity

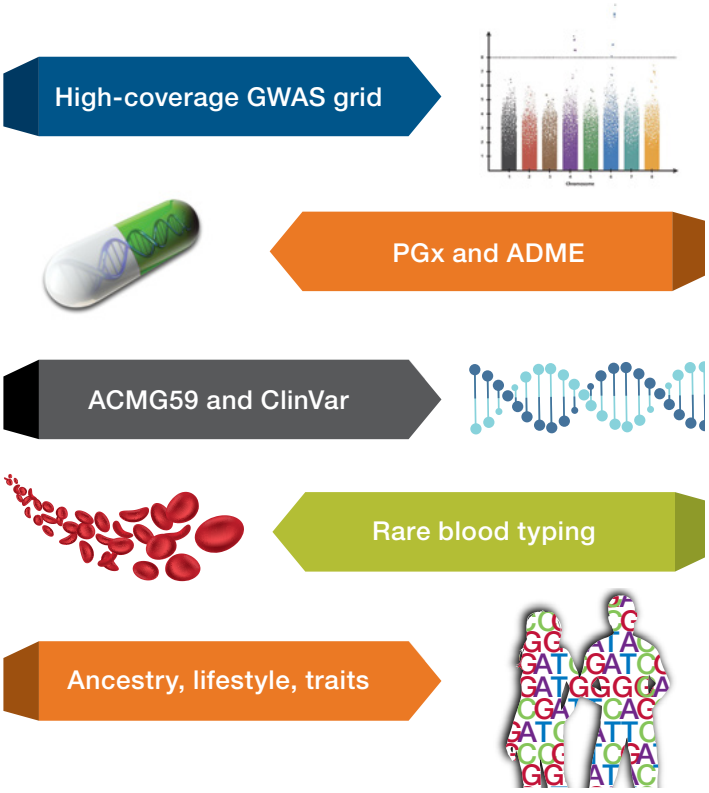

Figure 1. Key content on the Applied Biosystems™ Axiom™ Precision Medicine Diversity Research Array (PMD Research Array).

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Table 1. Content categories in the Axiom PMD Research Array compared with other catalog Axiom arrays.

Category	Description	Axiom PMD Research Array	Axiom PMR Array	Axiom Asia PMR Array	UK Biobank Axiom Array
GWAS module	Markers to maximize coverage in ancestral populations, especially in the 1–5% minor allele frequency (MAF) range, enabling cross-platform and cross-cohort metadata analysis	**>800,000**	>800,000	>540,000	>600,000
NHGRI-EBI GWAS Catalog	Includes content covering the complete NHGRI catalog of published GWAS as of June 2018	**>16,000**	>15,000	>23,400	>8,000
ACMG59	Markers from the list of 59 genes published by ACMG covering highly penetrant genetic disorders	**>15,000**	>11,000	>9,200	>9,000
ClinVar variants	Covers pathogenic or likely pathogenic associations from ClinVar archives (accessed June 2018)	**>24,000**	>23,000	>43,000	>7,500
High-value markers associated with inherited disorders	Markers in high-value genes such as *APOE* (Alzheimer's disease), *BRCA1/2* (breast cancer), *DMD* (Duchenne muscular dystrophy), and *CFTR* (cystic fibrosis) [4,5]	**>5,500**	>2,000	>2,000	>75
Pharmacogenomic (ADME)	• Number of ADME genes covered	**1,149**	661	962	932
	• Markers from PharmGKB (**pharmgkb.org**) with known relevance to drug metabolism	**>5,000**	>1,950	>2,600	>2,400
	• Total number of markers in ADME genes	**92,639**	49,643	69,988	67,197
Blood phenotypes and disorders	Covers variants that are used to identify the common and rare blood group types	**>1,100**	>550	>140	>650
Immunity, inflammation, and human leukocyte antigen (HLA)	Markers from HLA genes, killer cell immunoglobulin-like receptor (KIR) genes, and variants in research on specific autoimmune and inflammatory disorders, including ulcerative colitis, Crohn's disease, Graves' disease, Hashimoto's thyroiditis, and celiac disease	**>14,000**	>10,400	>10,400	>8,200
Cancer research risk variants	Over 10,000 cancer risk variants from the NHGRI-EBI GWAS Catalog, various publications, and the OMIM® database; includes variants associated with risks for colorectal [6], prostate [7], ovarian [8], lung [9], and gastric cancers, as well as typical blood cancers such as myeloma and lymphoma	**>10,000**	>10,000	>8,000	>6,500
Loss of function (LOF)	Markers to detect genetic changes that are predicted to completely disrupt the function of protein-coding genes, including rare and likely deleterious LOF alleles, predicted relevant variants, and common LOF variants in nonessential genes	**>3,100**	>33,000	>43,000	>30,000
Expression quantitative trait loci (eQTLs)	eQTLs with MAF >0.01% to support mapping functional noncoding variations to identify associations with gene transcription variability and differential gene expression	**>3,000**	>16,000	>15,000	>17,000
Neuropsychiatric conditions and lung function; CNV regions for developmental delay	Includes markers associated with increased risk for neurological conditions such as Alzheimer's and Parkinson's diseases, schizophrenia, and autism [10,11]	**>230**	>180	>910	>2,300
Fingerprinting and sample tracking	Includes fingerprint SNPs used by the University of Washington and the Broad Institute of MIT and Harvard; these markers are shared among several major genotyping platforms to facilitate sample tracking	**>300**	>300	>300	>300
Genetic testing	Includes a set of markers associated with lifestyle health conditions, most notably obesity, alcohol and smoking addiction, skin conditions, and asthma and allergies	**1,566**	1,221	1,232	288
Y chromosome markers	Markers on the Y chromosome that are suitable for applications covering deep ancestry	**>440**	>5	>400	>800
Mitochondrial markers	Common mitochondrial DNA variants	**>700**	>115	>500	>350
Total markers		**>900,000**	>900,000	>750,000	>800,000

GWAS grid

The Axiom PMD Research Array includes over 800,000 markers in the GWAS module. Common variants are intelligently selected via a proprietary imputation-based marker selection strategy for genome-wide coverage in the five major ancestral populations (Table 2). This process allows access to a vast number of rare markers (>1% MAF) and common markers (MAF >5%) for any given population, through imputation. The intelligent, imputation-aware design helps ensure that the selection of markers offers the highest imputation accuracy across all ancestral populations. The autosomal markers in the GWAS grid are valuable in ascertaining the ethnic breakdown of individuals genotyped with the Axiom PMD Research Array. Combined with the mitochondrial and Y chromosome markers, the Axiom PMD Research Array is a powerful array for determining ancestry and migration patterns in genetic testing [12].

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

	Number of imputed variants	Imputation accuracy*	
Population	**MAF >1%**	**MAF >1%**	**MAF >5%**
African (AFR)	14.7M	0.90	0.92
Admixed American (AMR)	10.1M	0.92	0.95
East Asian (EAS)	7.1M	0.87	0.92
European (EUR)	8.7M	0.92	0.95
South Asian (SAS)	8.5M	0.88	0.93

* Accuracy is the mean r^2 calculated across autosomal SNPs from the highest-ranked 900,000 markers.

ACMG59 and ClinVar

The Axiom PMD Research Array includes a set of markers covering 59 genes from guidelines published by the ACMG. The relevant variants in the ACMG59 genes identify and manage risk for selected highly penetrant genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality. More than 15,000 variants are selected on the Axiom PMD Research Array to interrogate the ACMG59 genes. These markers are known to be of high importance, such as those in the *BRCA1/2, CFTR, DMD,* and *APOE* genes. Advanced probeset designs for variants with very high GC content (>78%) in flanking sequences allow for accurate genotyping of such complex variants.

The Axiom PMD Research Array also includes variants from ClinVar archives curated for pathogenic or likely pathogenic significance. The module includes updated and well-annotated content from June 2018. ClinVar variants are crowdsourced by the scientific community. Pathogenic variants often carry information about the penetrability associated with the disease. A list of some of the disease research categories and number of associated variants is shown in Table 3.

Table 3. Markers of the Axiom PMD Research Array, classified into disease research categories and important subcategories according to OMIM and ClinVar databases.

Categories and subcategories	No. of markers
Cancer risk variants	**>10,500**
Myeloma	>45
Lung cancer	>100
Breast cancer	>4,000
Ovarian cancer	>5,600
Gastric cancer	>820
Leukemia	>550
Lymphoma	>240
Colorectal cancer	>3,600
Mental, behavioral, neurological, and neurodevelopmental risk variants	**>2,000**
Alzheimer's disease	>180
Parkinson's disease	>120
Schizophrenia	>445
Autism	>520
Inherited eye disease risk variants	**>250**
Macular degeneration	>95
Glaucoma	>45
Retinal dystrophy	>25
Retinitis pigmentosa	>130
Optic atrophy	>30
Autoimmune and inflammatory disease risk variants	**>450**
Celiac disease	>65
Crohn's disease	>370
Graves' disease	>32
Loss-of-function variants	**>10,000**
Autosomal recessive	>5,000
– Fanconi anemia	>3,000
– Cystic fibrosis	>240
– Thalassemia	>30
Autosomal dominant	>4,300
– Familial hypercholesterolemia	>1,600
– Mitochondrial diseases	>120
– Congenital conditions	>125
Cardiovascular disease risk variants	**>3,500**
Respiratory disease risk variants	**>1,000**
Diabetes risk variants	**>450**
Musculoskeletal disease risk variants	**>200**

Pharmacogenomics research

The Axiom PMD Research Array includes over 5,000 variants in 1,191 genes of known pharmacogenomic value [13]. This evidence-based content allows researchers to gain valuable insight into an individual's ability to process drugs based upon high, moderate, low, and preliminary scientific evidence. Figure 2 shows the distribution of the pharmacogenomic variants. The pharmacogenomics module includes:

- 1,200 core and extended functional pharmacogenomic research markers from Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines
- 1,098 markers in Very Important Pharmacogenes as identified by PharmGKB
- 260 markers in level 1 and level 2 categories that are of high and moderate significance
- 2,300 markers in level 3 and level 4 categories that are of low significance with research utility
- 1,936 markers from the Applied Biosystems™ DMET™ Plus Solution
- 33 markers in HLA genes associated with drug reactions

The Axiom PMD Research Array includes over 92,000 markers in ADME-associated genes, offering the highest density of any commercial array. The Axiom PMD Research Array used in conjunction with the Axiom 2.0 Plus Assay can unlock over 80 critical star alleles associated with highly predictive markers in genes including *CYP1A2, CYP2D6, CYP2B6, CYP2A6, SULT1A1, CYP2C19,* and *CYP2C8.* This unique assay opens up the ability to genotype these important pharmacogenomic markers that are in highly homologous regions of the genome. Based on gene-specific amplification, the Axiom 2.0 Plus Assay overcomes limitations observed in other hybridization-based microarray technologies, making it a unique array. CNV results are also presented in the software for *UGT2B17, GSTT1, GSTM1, CYP2A6* (3 regions), and *CYP2D6* (3 regions). The Axiom 2.0 Plus Assay workflow offers translation tables, and both comprehensive and phenotype reports to assist in generating reports associated with ADME responses for drugs.

Blood phenotypes and disorders

Common and rare blood groups are currently phenotyped using serological methods to identify antigens prior to blood transfusion or treatment. However, the disadvantages of these methods for phenotyping blood groups are well documented [14]. Cost, throughput, and reagent availability are the primary limitations of serology when performing full-donor matching. Blood groups are determined by genetic variants, so there is a need for a genotyping technology that offers the capability to genotype markers within these genes with high accuracy and repeatability. The Axiom PMD Research Array includes over 1,100 markers that can be used for typing the common blood groups (ABO, Rh, Kell) and rare blood groups to perform research in immunohematology, alloimmunization, and maternal–fetal incompatibility as well as in hemoglobinopathies.

The Axiom PMD Research Array leverages past efforts in the study of blood typing [15] and knowledge gained from the UK Biobank study [16] on the performance of blood typing using genotyping arrays. The blood module also includes research markers for anemia, bleeding disorders, and thalassemia. The large number of variants offers the ability to perform research in rare blood typing. The Axiom PMD Research Array offers the capability to genotype the *RHD* gene through the copy number genotyping capabilities of the platform.

Axiom technology has advantages over other array-based technologies because of the photolithographic manufacturing techniques. Bead-based technologies experience batch-to-batch variability and SNP dropouts with each manufacturing batch. The bead pools have a finite life even when manufactured in large batches, making the technology less reliable in clinical research applications where every marker is critical. The photolithographic manufacturing technology used in manufacturing Axiom genotyping arrays ensures 100% fidelity from array to array and batch to batch. All markers are present on every manufacturing batch, and the designs are available for the lifetime of the study—addressing a major concern for research studies that require every marker to be present on the array.

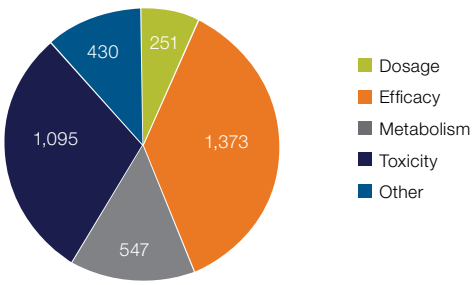

Figure 2. Distribution of ADME variants associated with drug response.

Applications in genetic testing

In recent years, genetic testing has evolved from using genomics to identify ancestry and lifestyle preferences to understanding risks associated with acquiring an inherited disease or condition. The successful completion of the UK Biobank study demonstrated that polygenic risk scores are relevant when considering disease risk.

The Axiom PMD Research Array includes markers for identification of ancestry for diverse populations, pharmacogenomics research, and rare blood typing. It includes additional genetic variants that have been identified in lifestyle phenotypes and traits such as diet, weight, metabolism, tastes, and more. The variants in the genetic testing module are shown in Table 4.

Table 4. Markers for genetic testing applications.

Lifestyle phenotypes and traits	Number of markers
Alcohol dependence and sensitivity	>140
Asthma	>250
Allergies	>60
Caffeine consumption	>30
Cholesterol levels	>35
Skin, hair, or eye pigmentation	>250
Smoking and addiction	>360
Vitamin absorption	>15
Weight and obesity	>900

Workflows for the Axiom PMD Research Array

The Axiom PMD Research Array introduces the Axiom 2.0 Plus workflow alongside the standard Axiom 2.0 workflow. The Axiom 2.0 workflow is a standard three-day workflow. Amplification through hybridization preparation is completed in two days. The Axiom 2.0 Plus workflow has an extra step introduced for gene-specific amplification for pharmacogenomic markers that are in highly homologous regions of the genome. The gene-specific amplification is performed in a clean room. The Applied Biosystems™ GeneTitan™ Multi-Channel Instrument automates array processing from target hybridization to scanning.

Applied Biosystems™ Axiom™ Analysis Suite software automates data analysis and includes allele-calling algorithms and user-friendly visualization tools. The analysis workflow as described in the Axiom Genotyping Solution Data Analysis Guide (Pub. No. 702961) enables high flexibility in finding the most informative content for each study. The Axiom PMD Research Array is enabled for copy number analysis in target regions as well as *de novo* genome-wide copy number discovery [17].

Specifications

Axiom PMD Research Array genotyping performance has been evaluated on 384 samples from the International HapMap Project using stringent quality control metrics that cover average sample call rate, sample concordance, and reproducibility. The array performance was also evaluated with 384 samples processed using the Axiom 2.0 Plus Assay to help ensure performance in regions of high sequence homology (e.g., markers in genes such as *CYP2D6*). Concordance and reproducibility were also evaluated on these markers (Table 5). The array performance using the Axiom 2.0 Assay was evaluated using 285 samples and is shown in Table 6.

Table 5. Performance of the Axiom PMD Research Array across 384 samples used with the Axiom 2.0 Plus Assay.

Metric	Specification	Performance
Number of samples	—	384
Sample pass rate	>95%	98.7%
Average call rate	≥99%	99.7%
Reproducibility	≥99.8%	99.9%
Average HapMap concordance	≥99.5%	99.8%
Average call rate of markers that require gene-specific amplification*	≥99%	99.8%
Concordance of markers that require gene-specific amplification*	≥99%	99.9%

* Applicable when used with the Axiom 2.0 Plus Assay.

Table 6. Performance of the Axiom PMD Research Array across 285 samples when used with the Axiom 2.0 Assay.

Metric	Specification	Performance
Number of samples*	–	285
Sample pass rate	≥95%	98.60%
Average call rate	≥99%	99.46%
Reproducibility	≥99.8%	99.92%
Average HapMap concordance	≥99.5%	99.79%

* 3 plates in the 96-array format were used for the evaluation, each with one control sample.

Microarray analysis is widely used in research on the polygenic nature of disease [18] because of its lower cost and ease of use in processing samples and analyzing genotyping data. The genotyping data from the UK Biobank study generated using the UK Biobank Axiom Array are available upon request to researchers, along with the deep phenotyping data. This allows data from the Axiom PMD Research Array to be used for replication of studies. With its comprehensive content, the Axiom PMD Research Array offers the functionality needed for large-scale precision medicine studies and genetic testing applications [19-21].

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Ordering information

Product	Description	Cat. No.
Axiom 2.0 Plus Assay, PMD Research Array, and GeneTitan Multi-Channel consumables kit	Sufficient for one 96-array plate (with reagents for multiplex PCR step)	951961
Axiom 2.0 Assay, PMD Research Array, and GeneTitan Multi-Channel consumables kit	Sufficient for one 96-array plate (without reagents for multiplex PCR step)	951962
Axiom 2.0 Plus Reagent Kit	Sufficient for one 96-array plate (with reagents for multiplex PCR step)	951960

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