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Assessing the utility of whole genome amplified DNA as a template for DMET Plus array

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Abstract

Background: Large amounts of high quality DNA are typically required for high-throughput genotyping arrays but sometimes study participant DNA is in limited supply. Multiple displacement amplification (MDA)-based whole genome amplification is an in vitro technique that permits the genetic analysis of limited amounts of high molecular weight genomic DNA (gDNA).
Methods: The performance of MDA-whole genome amplified DNA (wgaDNA) as a template for DMET Plus (Affymetrix) was assessed. wgaDNA was generated from gDNA from three HapMap CEU cell lines and 11 breast cancer patients. One HapMap sample and three patient samples were randomly selected for replication to assess reproducibility. Accuracy was assessed by comparing the wgaDNA genotypes with gDNA genotypes. The kappa (κ) statistic was used to measure genotype concordance between paired gDNA-wgaDNA and wgaDNA-wgaDNA samples. Copy number variants (CNV) were not included in concordance analysis in this study.
Results: A good genotype call rate of 98.8%±1.06% (mean±standard deviation, 1931 markers) was observed for all 18 wgaDNA samples with three samples having call rates lower than 98%. High genotype concordance rates were observed between four HapMap wgaDNA-gDNA pairs (98.5%, κ=0.9817, $p<0.0001$, 1931 markers) and 14 patient wgaDNA-gDNA pairs (100%, κ=1.00, $p<0.0001$, 19 markers among *CYP2D6* and *CYP2C19*). Excellent genotype concordance was also observed between four independently amplified duplicate samples (98.0%, κ=0.9745; $p<0.0001$, 1931 markers).
Conclusions: MDA-produced wgaDNA provides accurate and reproducible genotypes with the DMET Plus array and is therefore a suitable template for this targeted pharmacogenetic genotyping array.

Keywords: ADME; array; CYP2D6; DMET Plus; pharmacogenetics; pharmacogenomics; whole genome amplification.

Introduction

DNA arrays can be used to genotype millions of polymorphisms and copy number variants (CNV) in a single experiment. The technology can be applied to candidate gene and genome-wide association studies, as well as molecular karyotype analysis. The DMET Plus array (Affymetrix, Santa Clara, CA, USA) is a commercially available targeted genotyping array, specifically designed for pharmacogenetic applications. It genotypes 1931 common and rare polymorphisms and five CNVs among 225 genes that are of demonstrated importance to pharmacogenetics (1). The polymorphisms include 163 from the "Core List" of 32 genes that have been identified by the PharmaADME consortium of academic and pharmaceutical researchers to be of broad applicability to many pharmaceutical clinical trials and FDA drug submissions (www.pharmaadme.org).

The array employs molecular inversion probe (MIP) technology to assess multiple polymorphisms in a single, multiplexed assay with high accuracy and reproducibility (2). It requires a large amount of high quality DNA (1.02 μg) but as is the case for many genetic association studies, the amount of genomic DNA (gDNA) available for pharmacogenetic studies is often limited. Multiple displacement amplification (MDA) is an in vitro non-PCR-based whole genome amplification method that produces large amounts of whole genome amplified DNA (wgaDNA) from minute amounts of high molecular weight gDNA and reportedly does so with minimal locus or allelic amplification bias (3, 4). It is also reported to have better fidelity, higher average yields and larger DNA fragments (>10 kb) than other PCR-based whole genome amplification methods (5–7). MDA wgaDNA samples have previously been shown to give high genotype call rates and provide accurate genotypes with many low-, medium- and high-throughput genotyping platforms including the Affymetrix 10K SNP arrays (7), and Illumina GoldenGate BeadArray assays (Illumina, San Diego, CA, USA) (8) and two MIP arrays, including the Affymetrix 3K targeted genotyping system (9, 10). MDA may also permit the genetic analysis of limited amounts of gDNA with the DMET Plus array; however the DMET Plus varies from standard MIP arrays in that it

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performs an initial 36-plex multiplex PCR (mPCR) (11). This step uses locus specific primers that selectively amplify genes known to share high sequence identity with other genes, such as the CYP superfamily. It improves the genotyping accuracy of markers within these genes. Hence it is presently not known whether MDA-produced wgaDNA is a suitable template for the DMET Plus.

In the present study, we tested the accuracy and reproducibility of MDA-based wgaDNA as a template for the DMET Plus array, using wgaDNA generated from gDNA that was obtained from breast cancer patients.

Materials and methods

gDNA samples

gDNA was isolated from three HapMap CEU human cell lines (NA07357, NA11830, and NA11832, Coriell Cell Repositories, Camden, NJ, USA) and peripheral venous blood from 11 breast cancer patients using the QIAamp DNA Mini Kit (QIAGEN, Germantown, MD, USA), following manufacturer's instructions. The patient samples were collected from Lineberger Comprehensive Cancer Center Trial 0801. The DNA concentrations were determined using PicoGreen™ (Molecular Probes, Eugene, OR, USA), as per manufacturer's instructions. Informed consent was obtained from the cancer patients and the protocol was approved by the University of North Carolina Institutional Review Board.

Quality assessment of DNA samples

The quality of gDNA and wgaDNA samples was assessed by gel electrophoresis using a 0.8% agarose gel in TBE buffer (90 mM Tris-borate, 2 mM EDTA, pH 8.0), stained with SYBR® green I nucleic acid gel stain (SIGMA, St. Louis, MO, USA). Gels were visually inspected and samples with a clearly visible high molecular weight band (>10 kb) plus no smear or <10% of the DNA smeared on the gel were classified as grade 5 and 4, respectively, and considered suitable for MDA and DMET Plus genotyping. Samples with >10% smear on the gel (grade 3 or less) were not considered suitable for study. Images were visualized and photographed using the 300 nm ultraviolet transillumination of Biospectrum® multispectral imaging system (UVP, LLC, CA, USA).

Multiple displacement amplification

Genomic DNA from 11 breast cancer patients and three HapMap CEU cell lines were whole genome amplified by MDA using the REPLI-g® Mini Kit (QIAGEN), as per the manufacturer's instructions. Additionally, four gDNA samples were amplified in duplicate (one HapMap CEU and three patient samples) to assess the reproducibility of genotyping results. In brief, φ29 DNA polymerase was incubated with 20 ng of high molecular weight gDNA on a thermocycler (Tetrad 2, Bio-Rad, Hercules, CA, USA) at 30°C for 16 h. wgaDNA products were purified using the QIAamp® DNA Mini Kit (QIAGEN), in accordance with the manufacturer's instructions, and eluted with 200 µL distilled water. The eluent was evaporated to dryness in a rotary evaporator (Self-cleaning dry vacuum system, Gardner Denver Welch Vacuum Technology Inc., Niles, IL, USA) at room temperature for approximately 3 h and the residue was re-suspended in 30 µL 1×TE buffer (pH 8.0).

DMET Plus genotyping

Eighteen good quality, high-molecular weight wgaDNA samples, which included four sets of duplicates, and an Affymetrix-provided genomic control (gDNA) normalized to between 60 and 80 ng/µL (the DMET Plus reaction requires 17 µL of 60 ng/µL DNA), were genotyped by the DMET Plus array, as per the manufacturer's instructions (11).

Data analysis

Based on raw intensity signals stored in chip intensity files (.CEL), genotype calls were inferred using fixed boundary genotyping using DMET console 1.2 (Affymetrix) (12). The gDNA of the 11 patients were previously genotyped on the AmpliChip CYP450 system (Roche, CA, USA) by LabCorp (Laboratory Corporation of America, NC, USA) (13). This array genotypes 29 variants in the cytochrome P450 2D6 gene (*CYP2D6*), including two CNVs, and two major polymorphisms in the cytochrome P450 2C19 gene (*CYP2C19*) (14). Because the CNV data generated by DMET plus is not clinically useful in our particular patient samples, it was not included in statistical analyses.

Genotype concordance was assessed using Stata v11 (www.stata.org). Percent of genotype agreement (concordance) and kappa (κ) statistics (percent of agreement above and beyond chance alone) were calculated for polymorphisms from paired wgaDNA-gDNA HapMap samples (DMET Plus vs. DMET Plus), paired wgaDNA-gDNA patient samples (DMET Plus vs. AmpliChip CYP450) and four replicate samples (one CEU HapMap sample and three patient samples) (DMET Plus vs. DMET Plus) (15). No-calls and Possible Rare Allele (PRA) calls were included in the κ analysis. Affymetrix assigns PRA calls to genotypes that were rarely or not observed in assay development (11). One of the replicate pairs was randomly dropped and the genotype comparisons were performed. Since these tests are meant to be descriptive, all p-values are reported without corrections for multiple testing. To identify predictors of genotype failure, the Fisher's exact test was employed. $p<0.05$ was considered significant in this study. Data analysis was performed using Stata v11.

Results

The average yield (± standard deviation) of wgaDNA produced from 20 ng of gDNA was 5.5±0.39 µg (range: 4.9–6.4 µg) and the recovery following spin column cleanup was 43.6%±8% (range: 31.2%–58.3%). All 18 wgaDNA samples had high DNA quality scores (grade 4 and 5) suggesting the samples consisted of predominantly high molecular weight DNA with minimal degradation and were suitable for DMET Plus genotyping.

Genotype call rate

All wgaDNA samples were successfully genotyped by the DMET Plus array. The mean genotype call rate for all 18 wgaDNA samples was 98.8%±1.06% (range: 96.0%–99.8%). Three samples had call rates below 98%, which is the minimum acceptable call rate recommended by Affymetrix (11). Although the call rates were lower than the minimum call rate, they were satisfactory for providing usable genotypes for association studies.

DMET Plus genotype data for the three HapMap CEU gDNA samples was generated and provided by Affymetrix (16). The genotype call rates for all 1931 polymorphisms for the three distinct wgaDNA samples and one independently amplified replicate (98.7%±0.70%, range: 97.9%–99.6%) were not significantly different from the call rates previously obtained for the corresponding gDNA samples (100%±0.0%) (16) (paired t-test, p>0.05) (Table 1). The mean call rate of eight distinct wgaDNA samples plus three independently amplified replicates from patients was 98.9%±1.16% (range: 96.0%–99.8%).

Genotype concordance: patient samples

The AmpliChip CYP450 genotypes 29 polymorphisms in *CYP2D6*, including the CNVs, gene deletion (*CYP2D6*5*) and duplication (×*N*), and two major polymorphisms in *CYP2C19* (14). Nineteen polymorphisms were common to the AmpliChip CYP450 and DMET Plus arrays (Supplemental data, Table 1, accompanies the online version of this article at http://www.degruyter.com/view/j/cclm.2012.50.issue-8/issue-files/cclm.2012.50.issue-8.xml) and genotype agreement between paired patient samples was assessed to further test whether wgaDNA provides accurate genotype data on the DMET Plus array. Genotype calls were observed for all 19 polymorphisms and all samples on both platforms and 100% genotype agreement was observed between wgaDNA-gDNA pairs for *CYP2D6* and *CYP2C19* polymorphisms in 11 patient samples and three replicate samples. Additionally, κ analysis showed complete concordance between paired patient samples for all 19 markers (κ=1.00, p<0.0001) (Table 2).

Genotype concordance: HapMap samples

The genotype concordance for three distinct paired wgaDNA-gDNA HapMap samples and a replicate pair was 98.5%±0.77% (range: 97.6%–99.5%) (Table 1). κ Analysis indicated that there was very high concordance between the paired HapMap samples (κ=0.9817, p<0.0001) (Table 2).

The majority of genotype discordance was caused by no-calls or PRA calls and an improvement in genotype agreement was observed when no-calls and PRA calls were excluded (mean: 99.9%±0.09%, range: 99.8%–100%). Excluding no-calls, there was an average of two miscalls (±1.7, range: 0–4) between replicate samples and a total of seven miscalls among the four pairs (Table 1). Six miscalls were "gains of heterozygosity" and one was a "loss of heterozygosity." Gains of heterozygosity were observed for AM_10056 (*CYP2C19* rs17882687) in three of the four wgaDNA samples and AM_10090 (*CYP2C9* rs67807361) in two of them; both were non-core polymorphisms.

Reproducibility of wgaDNA samples

Genotype agreement between four duplicate wgaDNA samples was high with a mean of 97.9% (±0.98%, range: 96.6%–99.0%). κ Analysis also showed a high concordance between replicates (κ=0.9745, p<0.0001) (Table 2). The majority of discordant genotypes were caused by no-calls or PRA calls for one sample but not the other. Excluding no-calls and PRA calls, an improvement in genotype agreement was observed (mean: 99.8%±0.13%, range: 99.7%–99.9%).

Predictors of genotype failure

One hundred and seventy-five polymorphisms (9.1%) failed in at least one of the 18 wgaDNA samples and 75 polymorphisms (3.9%) failed in two or more samples. In an attempt to identify the polymorphisms most likely to fail on DMET Plus with wgaDNA as a template, we assessed whether no-calls were associated with polymorphism location or type, or mPCR. None of the markers were within 10,000 bp of a telomere or centromere, so proximity to telomeres and centromeres is unlikely to explain genotype failures. Seventy-seven of the 1931 markers are insertion/deletion polymorphisms (indels) and the rest are single nucleotide polymorphisms (SNPs) or other polymorphism types, e.g., small tandem repeats. Indels were not predictive of genotype failure (p=0.31, Fisher's exact test). The DMET Plus protocol includes an initial mPCR

Table 1 Genotype concordance between paired HapMap CEU wgaDNA and gDNA samples genotyped with DMET Plus.

	NA07357 gDNA[a]	NA07357 wgaDNA	NA11830 gDNA[a]	NA11830A[b] wgaDNA	NA11830B[b] wgaDNA	NA11832 gDNA[a]	NA11832 wgaDNA
Number of genotype calls	1931	1921	1931	1885	1903	1931	1900
Genotype call rate, %[c]	100	99.5	100	97.6	98.5	100	98.4
Number of no-calls	0	8	0	41	27	0	28
Number of PRAs	0	1	0	1	1	1	0
Number of mismatches (including no-calls and PRAs) (wgaDNA vs. gDNA)		10		46	28		31
Number of mismatches (excluding no-calls and PRAs) (wgaDNA vs. gDNA)		1		4	0		2
Genotype concordance (excluding no-calls and PRA), %		99.9		99.8	100		99.9
Number of "gain of heterozygosity"		1		3	0		2
Number of "loss of heterozygosity"		0		1	0		0

[a]Data obtained from Affymetrix. [b]Replicate samples were independently amplified. [c]The Affymetrix recommended minimum is 98%. N/A, not assessable; PRA, possible rare allele.

Table 2 Genotype concordance for paired samples (including no-calls and possible rare allele calls).

Sample type	wgaDNA vs.	Number of samples	Platforms compared (DMET Plus vs.)	Mean Concordance	κ	Standard error	p-Value
HapMap CEU	gDNA	3	DMET Plus	98.5%	0.9817	0.0062	<0.0001
Patient samples	gDNA	8	AmpliChip CYP450	100%	1.00	0.033	<0.0001
Replicate samples	wgaDNA	4	DMET Plus	98.0%	0.9745	0.0054	<0.0001

step to amplify loci that are in high sequence homology with other regions of the genome. This increases the genotyping specificity and accuracy of the array for markers of importance in these regions (2). Ninety-two polymorphisms were genotyped from these amplicons on the array. mPCR did not predict genotype failure either (p=0.85). We also evaluated whether polymorphisms in the PharmaADME core list polymorphisms were more or less likely to fail but found no relationship (p=0.20) (see Table 3 for a list of core polymorphisms that failed in at least one wgaDNA sample).

Discussion

In this study we assessed the performance of wgaDNA prepared by MDA on the commercially available DMET Plus array. Our data show that MDA wgaDNA prepared from high molecular weight gDNA is a satisfactory substitute for gDNA as a template for the DMET Plus array. Although the percent of called genotypes tended to be lower for amplified than unamplified DNA samples, the genotype concordance rates between gDNA and wgaDNA samples, when no-calls and PRAs were excluded, were excellent (99.9%), suggesting wgaDNA provides reliable and accurate genotypes.

MDA-based wgaDNA has been previously tested as a template on several genome-wide array chips. Using blood DNA as a template for MDA, Cormier and her colleagues observed a mean call rate of 95.1% for wgaDNA and 99.2% concordance between amplified and unamplified samples with the Affymetrix 3K Targeted Genotyping system (9). wgaDNA has also been successfully genotyped with other Affymetrix array systems, including Affymetrix 10K SNP Arrays (7) and Affymetrix Mendel Nsp 250K chip (17). However, when genotyped with the Affymetrix Genome-Wide Human SNP Array 6.0, a significantly lower call rate of 45%±2.7% was obtained for amplified compared with 98%±1.1% in unamplified samples (18). Considering Illumina arrays, over 2000 wgaDNA samples have been tested on the GoldenGate BeadArray and the mean call rate and concordance were >99% (8).

"Loss of heterozygosity" (AB→AA or BB) was identified in a previous study as the major source of discordant polymorphisms between amplified and unamplified samples (18). The majority of miscalls in the present study were due to no-calls. Upon exclusion of no-calls and PRAs, the most common source of discordance was "gain of heterozygosity" (AA or BB→AB) (Tables 1 and 4). A possible explanation for loss or gain of heterozygosity observed in the present study could be that the genotype signal of HapMap wgaDNA samples differed from the genotype signal of HapMap gDNA samples in Affymetrix development studies, which was used to set the boundaries for calling genotypes.

Some studies have shown proximity to telomeres and centromeres and a higher GC percentage of the flanking sequences (secondary structure) significantly increases the rate of genotyping failures of wgaDNA (19). Centromeres and telomeres are highly repeated regions and only a few random primers in the REPLI-g amplification mix can prime within these regions. Therefore, during MDA, centromeres and telomeres have low yield or drop out. According to the data generated by QIAGEN, the output of genes within 5000 bases of these poorly amplified regions can be affected; otherwise, it should not be a problem (20). The polymorphisms genotyped by DMET Plus are not close to the telomeres or centromeres, so their chromosomal position is unlikely to

Table 3 Summary of PharmaADME core polymorphisms that failed in at least one of 18 wgaDNA samples.

DMET Probe ID	Gene	Reference sequence identifier	Common allele name	Number of no-calls	Number of PRA
AM_13024	*UGT1A1*	rs34815109	UGT1A1*28	8	0
AM_11005	*SULT1A1*	rs9282861	R213H	4	0
AM_14348	*SLC22A1*	rs12208357	R61C	4	0
AM_11012	*SULT1A1*	rs72547527	R37Q	3	2
AM_10128	*CYP2C8*	rs11572103	I269F	2	0
AM_10762	*CYP1A1*	rs1800031	3204T>C	2	0
AM_13980	*TPMT*	rs1800460	A154T	1	0
AM_10135	*CYP2C8*	rs11572080	R139K	1	0
AM_10496	*SLCO1B1*	rs2306283	N130D	1	0
AM_14363	*SLC22A1*	rs628031	M408V	1	0

PRA, possible rare allele.

Table 4 DMET Plus genotypes discordant between paired HapMap CEU gDNA and wgaDNA samples.

DMET probe set ID	Gene	Reference sequence identifier	Chromosome	Sample ID	gDNA genotype[a]	wgaDNA genotype	Gain of heterozygosity	Loss of heterozygosity
AM_10056	*CYP2C19*	rs17882687	10	NA07357	A/A	A/C	3	0
				NA11830A, B	A/A	A/C, no-call		
				NA11832	A/A	A/C		
AM_10090	*CYP2C9*	rs67807361	10	NA07357	A/A	no-call	2	0
				NA11830A, B	A/A	A/C, no-call		
				NA11832	A/A	A/C		
AM_10430	*GSTP1*	rs8191439	11	NA07357	G/G	G/G	1	0
				NA11830A, B	G/G	A/G, G/G		
				NA11832	G/G	G/G		
AM_10591	*ATP7B*	rs1801246	13	NA07357	G/G	G/G	0	1
				NA11830A, B	A/G	G/G, A/G		
				NA11832	G/G	G/G		

[a]Genotypes obtained from Affymetrix.

predict genotyping failures. We were unable to assess GC content of the flanking sequences but did investigate polymorphism type, and mPCR and found neither factor was predictive of genotype failure.

Some limitations of the study should be considered; mostly the limited sample sizes used to assess call rates (18 wgaDNA samples), accuracy and reliability (four pairs of wgaDNA-gDNA, including one replicate pair), and reproducibility (four independently amplified duplicates). Also, we compared wgaDNA genotypes with the genotypes of the corresponding unamplified samples, which were generated by another laboratory and part of the training set that was used to define the genotyping cluster boundaries. Despite the limitations of this study, we believe that the results we obtained provide evidence that MDA wgaDNA is a suitable substitute for gDNA with DMET Plus.

In summary, our results showed that MDA-wgaDNA, produced from good quality gDNA, performed with high accuracy and reproducibility on the DMET Plus array. Thus, we anticipate that this method can be successfully applied to pharmacogenetic studies of good quality DNA samples that are in short supply.

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Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. Research support played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.
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