The OncoArray Consortium: a Network for Understanding the Genetic Architecture of Common Cancers

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Abstract

Background—Common cancers develop through a multistep process often including inherited susceptibility. Collaboration among multiple institutions, and funding from multiple sources, has allowed the development of an inexpensive genotyping microarray, the OncoArray. The array includes a genome-wide backbone, comprising 230,000 SNPs tagging most common genetic variants, together with dense mapping of known susceptibility regions, rare variants from sequencing experiments, pharmacogenetic markers and cancer related traits.

Methods—The OncoArray can be genotyped using a novel technology developed by Illumina to facilitate efficient genotyping. The consortium developed standard approaches for selecting SNPs for study, for quality control of markers and for ancestry analysis. The array was genotyped at selected sites and with prespecified replicate samples to permit evaluation of genotyping accuracy among centers and by ethnic background.

Results—The OncoArray consortium genotyped 447,705 samples. A total of 494,763 SNPs passed quality control steps with a sample success rate of 97% of the samples. Participating sites performed ancestry analysis using a common set of markers and a scoring algorithm based on principal components analysis.

Conclusions—Results from these analyses will enable researchers to identify new susceptibility loci, perform fine mapping of new or known loci associated with either single or multiple cancers, assess the degree of overlap in cancer causation and pleiotropic effects of loci that have been identified for disease-specific risk, and jointly model genetic, environmental and lifestyle related exposures.

Impact—Ongoing analyses will shed light on etiology and risk assessment for many types of cancer.

Keywords

Genetic Susceptibility; Genetic Epidemiology; Ancestry; Epistasis; Cancer

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Introduction

Cancer is one of the leading causes of death world-wide. In 2012 the estimated number of cancer cases around the world was 14.1 million; and this number is estimated to swell to 21 million by 2030(1). Cancer has a sizable heritable component. A large twin study estimated that heritable factors may explain between 20% and 40% of the variance in cancer risk(2). High-penetrance mutations, including those in *BRCA1* and *BRCA2*, *APC* and DNA mismatch-repair genes, are estimated to account for less than 5% of all cases(3, 4). As for other common complex diseases, it is expected that much of the inherited susceptibility to cancer is likely to be explained by common alleles having low-penetrance(2–5). Large consortial efforts may identify effects from additional rarer alleles (6, 7). As pointed out by Ponder (8, 9) and Peto(10) common genetic variants account for a large proportion of cancer incidence, even though they do not individually lead to strong clustering within families. Moreover, the combinations of effects from genetic and environmental factors may account for substantial differences in cancer susceptibility within and among populations(8–13).

Over the past decade, genome-wide association studies (GWAS) of cancer have discovered multiple low-penetrance loci. Given that the effect sizes are generally weak (relative risks per allele of 1.3 or less), increasing the sample size has become crucial in identifying and characterizing true genetic associations. Genetic signatures of cancer etiology indicated novel influences in cancer development, thereby providing new insights into etiologic mechanisms that suggest interventions (14). By identifying many new loci influencing cancer development, genomic research has identified pathways that influence cancer development(15). In addition, Mendelian randomization has emerged as an effective approach for confirming non-genetic etiologic factors identified through epidemiologic studies, removing potential concerns about reverse causality(16).

Once the loci are identified, fine-mapping studies are a critical next step in finding functional variant(s) and in the discovery of nearby, independent, secondary signals, which may increase the heritable fraction explained by each region. More than 90% of risk-alleles lie in non-protein coding DNA and there is now unequivocal evidence that risk regions are enriched for regulatory elements, including enhancers, promoters, insulators and silencers(17). In general, genome-wide estimates in humans indicate about 500,000 enhancers may alter regulation of expression and thus alter risk by controlling expression of target susceptibility genes(17–20). Analyses to date indicate that several regions harbor multiple distinct susceptibility variants for different cancer types, suggesting common mechanisms but tissue-specific regulation(21). Thus fine-mapping of multiple cancer types using a common array is likely to be an effective strategy for finding new alleles influencing common cancers and for unravelling mechanisms in their etiology.

The overall goal of the OncoArray Consortium is to gain new insights into the genetic architecture and mechanisms underlying common cancers, by deploying a new genotyping array, the OncoArray, and using it to genotype a large number of cases with cancers of the breast, colon, lung, ovary, prostate or endometrium as well as genetically susceptible individuals such as *BRCA1* and *BRCA2* mutation carriers along with a large number of cancer-free controls. The collaboration arose, in part, through the efforts of the Genetic

Associations and Mechanisms in Oncology (GAME-ON) consortium, which was a multi-year project to characterize SNP associations for common cancers and to understand their mechanistic and functional consequences in disease development. The OncoArray project provides an unprecedented opportunity both to discover new cancer susceptibility variants, common and rare, and to identify the likely causal variants at known loci through fine mapping and the integration of disease associated variants with tissue-specific regulatory information. Additionally, joint genotyping across cancer sites permits sharing of controls and a more comprehensive assessment of genetic risk among many cohort studies that participated in this study. Moreover, given the evidence that some of the loci influencing cancer risk are shared among cancer sites, the genotyping of a common array across multiple cancer sites provides an excellent opportunity to study the pleiotropic effect of susceptibility loci. However, while there is tremendous value in organizing a genotyping consortium on this scale, there are also substantial challenges in how best to integrate data across this diverse spectrum of cancer sites and genotyping locations. To facilitate the analysis, the consortium developed shared procedures for genotype calling and quality control. This report describes the development of the consortium, the array that was designed, and quality control approaches that have been implemented across the consortium.

Materials and Methods

Principles in sample and SNP selection

The OncoArray Consortium is focused on the discovery of variants influencing common cancers, in particular cancers of the breast, colon, lung, ovary, and prostate. These cancers were chosen for analysis based upon prior observation of some common causal pathways(15) as well as the opportunity provided by common funding through the GAME-ON, a consortium of U19 grants studying genetic etiology of breast, ovarian, prostate, colon and lung cancers. The existence of an effective, multi-consortium collaboration provided an opportunity primarily because of economies of scale. The potential to utilize common control sets across the consortia gave added value. A description of the sample sets is provided in Supplementary Tables 1a–1g. Endometrial cancer cases were included because endometrial cancer shares several risk factors with breast cancer and ovarian cancer, such as the genetic locus (*HNF1B*) which has shared variants with prostate (22, 23) and ovarian cancer(24). Finally, there are similarities in tumor phenotype and/or shared tissue of origin between endometrial cancer, the benign gynaecological condition endometriosis, the endometrioid and clear cell histologies of ovarian cancer, and basal-like breast cancer(25–27). Thus, pooling ovarian and endometrial(23, 28, 29) cases could uncover novel loci.

The array was designed from a final list of approximately 600,000 markers, of which approximately 533,000 were successfully manufactured. Of these, nearly 50% of the markers were selected as a GWAS backbone (Illumina HumanCore). These markers were selected to tag the large majority of known common variants, via imputation. The remaining markers were selected from seven lists: five from the disease consortia representing the main cancer sites, one from the CIMBA consortium including potential modifiers of cancer risk in *BRCA1* or *BRCA2* carriers, and a seventh "common" list that included variants of common interest (see below). SNPs were allocated to these disease sites, and to CIMBA, according to

the number of samples that each consortium would be contributing. In addition, the array that was configured by Illumina allows flexibility for cancers not originally participating in the design of the array by allowing additional custom content to be added to the array. The general principles for SNP allocation were set by consensus by members of the OncoArray Consortium as presented in Table 1. More detailed descriptions of the SNP selection process for disease sites participating in the OncoArray are also provided in the Supplementary Methods and governance described in Supplementary Information about the Oncoarray Consortium. Below, we present the general approaches that were taken for nominating SNPs for the Array.

Selection of SNPs for inclusion within disease site

SNPs to be included in the array were nominated by participating consortia organized into each of the major disease site groups that participated in the primary array development. Each cancer site used its own prioritization scheme. Generally, selection of SNPs were based on 1) candidate SNPs from loci enriched showing some evidence of association (e.g. $p<10^{-5}$) from previous GWAS of common cancers (breast, ovarian, prostate, colon and lung) (30–37); 2) fine mapping of risk loci based on 1000 Genomes Project data and resequencing studies(38); 3) candidate rare variants from whole genome and whole exome studies, and exome arrays(39); 4) findings from previously published studies of other cancers provided by the NHGRI SNP catalogue (40) and other online resources; and 5) other "wild-card" variants, for example variants of potential functional significance(18, 41, 42). The majority of SNP selection was based on regions previously identified from GWAS in European populations, but disease sites also allocated tagging SNPs to capture variability for Asian and African descent populations. In addition to site-specific variants, some of which were nominated by more than one group, candidates were nominated from *in silico* functional analyses that suggested putative mechanistic targets for risk variants based either on their predicted effects on the coding sequence of candidate genes, or their intersection with non-coding, putative regulatory targets (see below). Finally, variants associated with phenotypes that correlate with cancers (such as smoking or BMI) were also selected.

Selection of SNPs for fine-mapping

Similar procedures were followed for each site. We first defined a 1Mb interval surrounding the known lead signal for each genome-wide signal. Where such regions overlapped, the intervals were amalgamated into a single interval so as to include 500kb either side of each hit. Common regions were defined as regions including hits within 1Mb for more than one cancer type, amalgamated as described. We then identified and obtained design scores for all variants in the interval from the 1000 Genomes Project (phase I version 3, March 2012 release). From among designable SNPs, we then selected three sets of variants (1) all variants correlated with the known hits at $r^2>0.6$, (2) all variants from lists of potentially functional variants, defined through RegulomeDB and (3) a set of SNPs designed to tag all remaining variants at $r^2>0.9$.

Selection of "Common" SNPs

Previous analyses(30, 32, 43, 44) have demonstrated that association signals for different cancers tend to cluster together, perhaps reflecting common mechanisms. For this reason, we

selected a dense set of SNPs within 1Mb (see above) across all regions in which this occurred for more than one cancer type. Variants were nominated for inclusion if they, i) occurred within genes that have been found to associate with pharmacogenetic traits relevant to cancer, ii) had previously been associated at genome-wide levels of significance for any other cancer type (not among the five primary cancers sites participating in the OncoArray Consortium) as defined by the GWAS Catalog (45) and iii) had been found to be relevant to cancer associated traits(46) including BMI, height, and waist to hip ratio (in collaboration with the GIANT consortium(47), smoking, age at menopause or menarche (in collaboration with the REPROGEN consortium(48), and telomere length in lymphocytes(31). We also included additional SNPs that showed evidence of association with other cancer types including endometrial, testis, bladder and pancreatic cancer, Wilms' tumor, and glioma, and SNPs tagging known common eQTLs (i.e. associated with expression across a range of tissues).

Pharmacogenetic variants were nominated by several collaborators based on i) functional variants in 19 genes nominated by the pharmacogenetics network, ii) functional variants or tagging SNPs in CYP2A6 and CYP2B6 and iii) SNPs nominated by PharmGKB and variants nominated from study of cell lines to affect expression of pharmacogenetically relevant genes. (49) SNPs from the region of chromosome 15q25.1 that associate with lung cancer and smoking behavior were placed in the common region given the ubiquitous effects of smoking on cancer risks. Of note, *BRCA1* and *BRCA2* were finally released from patent controls two days before the final selection of SNPs so that common functional variants of these loci could be included in the array. We included additional (non-polymorphic) probes for each exon of *BRCA1*, *BRCA2*, *MLH1* and *MSH2* in order to capture large deletions in these genes. Finally, we included a panel of Y chromosome and mitochondrial markers to provide data on population ancestry.

The Division of Cancer Epidemiology and Genetics of the National Cancer Institute accumulated GWAS scan data for other cancer sites including bladder, NHL (Non-Hodgkin's Lymphoma), esophageal, gastric, glioma, kidney, osteosarcoma, pancreas, testis or scan data for non-Caucasian studies including Asian non-smoking female lung cancer and African American lung cancer. The top 200–400 most significant loci from each scan were selected after ranking by association test p value and LD pruning ($r^2 > 0.6$).

Functional characterization and selection—Risk variants at known susceptibility loci for breast, colorectal, lung, ovarian and prostate cancer were integrated with epigenomic datasets from ENCODE and other published sources, to identify intersections between risk SNPs and tissue-specific regulatory features that define the most likely causal variants and their functional targets. We interrogated associations between SNPs and DNAse Hypersensitivity (DHS) sites generated in the pan-cancer cell line panel from ENCODE, as well the LNCaP cell line (for prostate cancer specific marks), the HMEC line (for breast), the SAEC line (for lung cancer), the HCT116 line (for colorectal cancer) and the CaOV3 line (for ovarian cancer). The most likely causal SNPs from these analyses were prioritized in the selection of fine mapping variants described above. In addition, we identified candidate causal SNPs at loci associated with risk of two or more cancers, to identify the putative functional targets that are common across cancer types as well as those are

tissue/cancer specific at these loci. A summary of these analyses are illustrated in Figure 1. This approach evaluates regions around the significant SNPs common to cancers to identify regional variants that impact chromatin structure, expression levels or transcription factor binding sites to enrich for SNPs directly related to cancer development.

Pruning and merging procedures

As a starting point, we "forced-in" all SNPs in the GWAS backbone (260,660) and the common fine-mapping list (32,548). All other lists include SNPs that passed design at Illumina and were rank ordered with the most important SNPs first, and were pruned to exclude redundant SNPs in LD ($r^2 > 0.9$) with other SNPs in the same list or the "force-in" set described above.

The proportions allocated to each disease site are listed in the Supplementary Table 2.

The final merging took the lists of SNPs generated by the disease sites and for common mapping and generated a single list in the following order:

   a.   Include the GWAS backbone

   b.   Include the Common fine-mapping list

   c.   Choose the remaining SNPs iteratively from the five ranked lists. At each stage choose the next SNP from the list with the smallest value of n/p, where n is the number of SNPs already chosen from that list and p is the proportional allocation of that list, as given in the above table. This ensured that the correct proportions were kept.

   d.   Include the SNP unless the exact SNP has already been chosen. In either case, augment the count n for that list by 1.

   e.   Increase the number of beadtypes for chosen SNPs, where necessary because variation could not be captured by a single beadtype.

Based on the merged list of 715,637 unique SNPs (76,290 from lung; 224,074 from familial and sporadic breast and ovarian; 81,009 from prostate; 50,110 from colorectal; 17,547 from common list), we further performed LD pruning ($r^2 > 0.95$). This process resulted in a total of 651,216 SNPs. A set of obligatory SNPs provided by each contributing lists was not allowed to be "pruned".

After this process, we submitted 568,712 SNPs (reaching the total number of ~600,000 beadtypes) from the priority lists to Illumina for manufacturing. Of these, a total of 533,631 (93.8%) passed quality control procedures and were included as valid markers on the array.

Genotyping

To minimize variability that might result from genotyping among sites and to improve efficiency, the large majority of genotyping was performed at just 8 sites CIDR (n=211,638), Cambridge (n=98,770), Genome Quebec/McGill Innovation Center (n=55,121), the National Cancer Institute (26,803), the Mayo Clinic (n=22,023), Denmark (n=5,961), and Shanghai

(n=3,840). To ensure comparability among centers, selected Hapmap samples were analyzed by all groups.

Quality control steps

A detailed quality control plan was developed and is included as Supplementary material but salient features are presented here. Participating sites genotyped a common set of Hapmap samples so that strand alignment and integrity of imputation could be compared among analytical sites. All sites used a common genotype clustering file that can be downloaded from http://consortia.ccge.medschl.cam.ac.uk/oncoarray/onco_v2c.zip and removed 765 duplicated probes (onco_duplicate_variants_excluded.csv).

Clustering process

A selection of 56,284 samples with high call rates from across the genotyping centers were combined into a single Illumina Genome Studio project and automatic clustering performed using the GenTrain 2 clustering algorithm. This included 3,687 African-American, 5,590 Asian and 2,608 Hispanic samples. A large number of samples was used to increase the chances of including heterozygotes for the many rare variants on the array (23,249 variants have a MAF below 0.0005). Variants showing poor clustering (57,673) were manually evaluated and revised, which reduced the number to 16,526 variants excluded from the analysis.

Ancestry Analysis

Ancestry analysis was performed using a standardized approach in which 2,318 ancestry informative markers (AIMs) with minor allele frequencies of 0.05 or higher were used on 66,105 samples genotyped at CIDR, Cambridge and Genome Quebec/McGill Innovation Center (the primary contributing centers) and 505 Hapmap 2 samples. We noted that among those individuals not clearly aligning into one of the major continental ancestry groups there are clines connecting ancestral groups along axes connecting the centroids of the ancestral populations. We mapped ancestry to regions of a triangle connecting the three regions, in order to estimate the contribution of European, Asian and African ancestry to each individual. The method is further described in the software package FastPopc(50) distributed to consortium members. Individuals were thus classified into 4 groups for downstream analyses: European (defined as >80% European ancestry), Asian (>40% Asian ancestry), African (>20% African ancestry) and other (not fulfilling any of the above criteria) (50) (see Supplementary methods).

Results

Genotyping quality

Samples passed genotyping quality control steps if more than 95% of SNPs had valid calls. After manual review of cluster plots for SNPs failing to achieve 95% call rates a total of 494,763 SNPs were retained for analysis. The call rate varied according to tissue source and DNA processing steps (Figure 2). Overall, 97% of samples had call rates of 95% or higher. However, the efficiency in genotyping varied markedly among sources of DNA. In particular, genotyping of samples derived from peripheral blood provided excellent

performance with a 98% success rate, while amplified DNA derived from non-blood samples show poor performance (18% overall failure rate for amplified buccal or saliva). The success rate for genotyping Hapmap derived samples was 100% and the overall genotyping success rate for lymphoblastoid lines was 99.5%.

Analysis of concordance of sample genotypes

To evaluate the reliability of genotyping across samples including post-imputation processing we evaluated concordance of imputed SNP genotype probabilities among the centers. Figure 3 depicts average squared correlations among 19,367,932 variants imputed from v3 of the 1000 Genomes Project for Hapmap samples genotyped and imputed in Cambridge versus the same samples genotyped by CIDR and imputed at Dartmouth using the same imputation protocol (Supplementary methods). The integral values along the X axis depict results for the same individual, with multiple replicate samples having been genotyped for individuals 1, 4, 5, 6 and 8. Samples 1–8 derive from European descent individuals, samples 9–10 are Chinese, sample 11 is Japanese and samples 12–14 are Yoruban. Correlations in genotypes performed at different centers were high but were slightly higher for European descent samples (average $R^2=0.985$) versus Chinese (average $R^2=0.958$), Japanese (average $R^2=0.961$) or Yorubans (average $R^2=0.975$). Supplementary Figure 1 compares the imputation accuracy of the OncoArray to several other arrays.

Discussion

Comparison to other large-scale genotyping efforts

The OncoArray is a scientific community-derived effort from many world-wide investigators to understand common causes of cancer susceptibility and progression. The array that was configured balanced several needs. First, each of the contributing groups had specific interest in fine mapping and validation of previously suggested loci. This element of the OncoArray is similar to prior large-scale consortia such as the Metabochip (51) and the Immunochip(52), which are highly targeted arrays. Balanced against the fine mapping element, we also allocated about 50% of the array to permit further discovery of novel variants. The array balances the needs for new discovery with validation and fine mapping; it is unlike prior arrays such as the Metabochip or Immunochip which did not include a GWAS array backbone. More generic platforms such as the Biobank array can be applied for a broad range of diseases but did not include content specific for known cancer loci. The OncoArray, thus, has broad value for studying cancer or related conditions. Additionally, the platform allows additional content to be added so that other scientists or consortia such as Gliogene or Pancan could add content specific to their cancer types with minimal additional cost.

Impact of Findings on Prevention and Treatment

We expect the discovery of novel genetic risk factors for cancer to provide insight into the genetic architecture of cancer and help elucidate its underlying biology. Providing a more comprehensive list of loci strongly associated with cancer susceptibility will greatly increase our knowledge of the pathophysiology of early stages in cancer development.

The clinical value of genetic testing for SNPs was questioned by some commentators because individual variants have limited power to discriminate cancer risk(53, 54). However, modeling show analysis with multiple variants provides discrimination in risk stratification sufficient to improve the efficiency of screening (55), as born out by recent studies. For example, Pashayan and colleagues(56) showed that if prostate cancer screening were offered to men with a ten-year absolute risk of greater than 2% then risk stratification based on age and a 31-SNP polygenic risk score would result in 16% fewer men being eligible for screening than risk stratification based on age alone, but only 3% fewer cases would be detected(56). So and colleagues(57) showed that a polygenic risk model allows more precise enrollment of women according to age reducing the cost and burden of mammography. Given the expense and potential harms associated with prevention and early diagnosis (e.g. overdiagnosis and false positive findings) identifying those at highest risk might have important public health implications. These examples demonstrate the potential of genetic findings(58, 59) to impact public health and clinical care through the next several decades(60).

Gene-environment Interactions (GxE)

Several environmental and lifestyle risk factors, many of which are modifiable, such as obesity, physical activity, non-steroidal anti-inflammatory drug (NSAID) use, hormone use, diet, smoking, and alcohol have been associated with various cancers. To fully understand the impact on the etiology of cancer, it is important to examine whether the genetic factors modify the effect of environmental factors. Recently there has been extensive methodologic and applied work that provides a strong rationale for examining GxE interactions(8, 10–13, 61–65). The development of statistical methods for genome-wide GxE with increased power (66, 67) has led to detection of genetic variants whose effects are modified by environmental factors; and identification of variants that would have been missed through searches of marginal effects alone. As genetic profiles are fixed, modifying environmental exposures to alter deleterious effects of alleles remains the most viable preventive strategy. Importantly, even in the absence of gene-environment interaction on the multiplicative scale, the absolute reduction in risk due to a change to a lower risk lifestyle is greater in those at higher genetic risk, making the development of tools to predict genetic risk a critical component of advice on lifestyle risks. Additionally, the application of large scale genetic testing of the same platform on a very large number of individuals permits an unprecedented opportunity for studying the impact that epistasis, interaction among loci, has upon risk for cancer development.

Functional characterization of risk loci

Perhaps the greatest challenge facing large collaborative genotyping projects such as the OncoArray is to understand of the functional mechanisms underlying disease development at each susceptibility locus. The pace of discovery of genetic risk associations for cancer and other traits and diseases continues to accelerate, creating an increasing bottleneck between discovery and functional validation. The basic tenets of functional characterization(68) – proving causality for risk variants and the genes they regulate - have been described for a tiny fraction of risk associations identified by GWAS(20, 69). This is partly due to our rudimentary knowledge of the non-coding genome and the effects of genetic variation on

gene regulation. Integration of GWAS SNP data with methylome data has identified methylation-quantitative trait loci (meQTLs) showing that inherited genetic variation may affect carcinogenesis by regulating the human methylome(70, 71). The ENCODE (**ENC**yclopedia **O**f **D**NA **E**lements) consortium has catalogued genome-wide regulatory elements for many, but by no means all human tissues(72). Enhancers are often cell type-specific and drive the spatial and temporal diversity of gene expression in and across different cell types (73). One of the main challenges will therefore be to define the regulatory landscape for the relevant cell type for each trait-associated locus, followed by integration with genetic fine mapping data to identify the most likely regulatory targets.

The ability to test the function of specific risk alleles has been enhanced by recent developments in genome editing, a powerful and highly efficient methodology for introducing DNA sequence alterations in human cells. Engineered nucleases (e.g. the CRISPR-Cas9 system) with customizable cleavage specificities can be used to introduce induce precise DNA base substitutions at the site of risk SNPs. The molecular and phenotypic effects of the different alleles of each risk SNP can then be evaluated *in vitro* or *in vivo*. The success of genome editing has been recently demonstrated for GWAS risk variants associated with fetal hemoglobin and prostate cancer. (69, 74)

Complementary to genome editing for proving causality of risk SNPs is expression quantitative trait locus (eQTL) analysis to identify the likely target susceptibility gene(75, 76). eQTL analyses can interrogate both near and distant regulatory associations between risk genotypes and gene expression on the same chromosome (*cis-*) or across chromosomes *(trans-)*. The role of these genes in neoplastic development can then be evaluated in experimental models of disease(77). Many groups have applied this concept to identify transcript expression correlated with trait-associated SNPs(78–80). For example, GAME-ON investigators have successfully used eQTL analysis to identify susceptibility genes at several breast, prostate and ovarian cancer loci, and confirmed the significance of these genes through their functional analysis in disease models(42, 81, 82).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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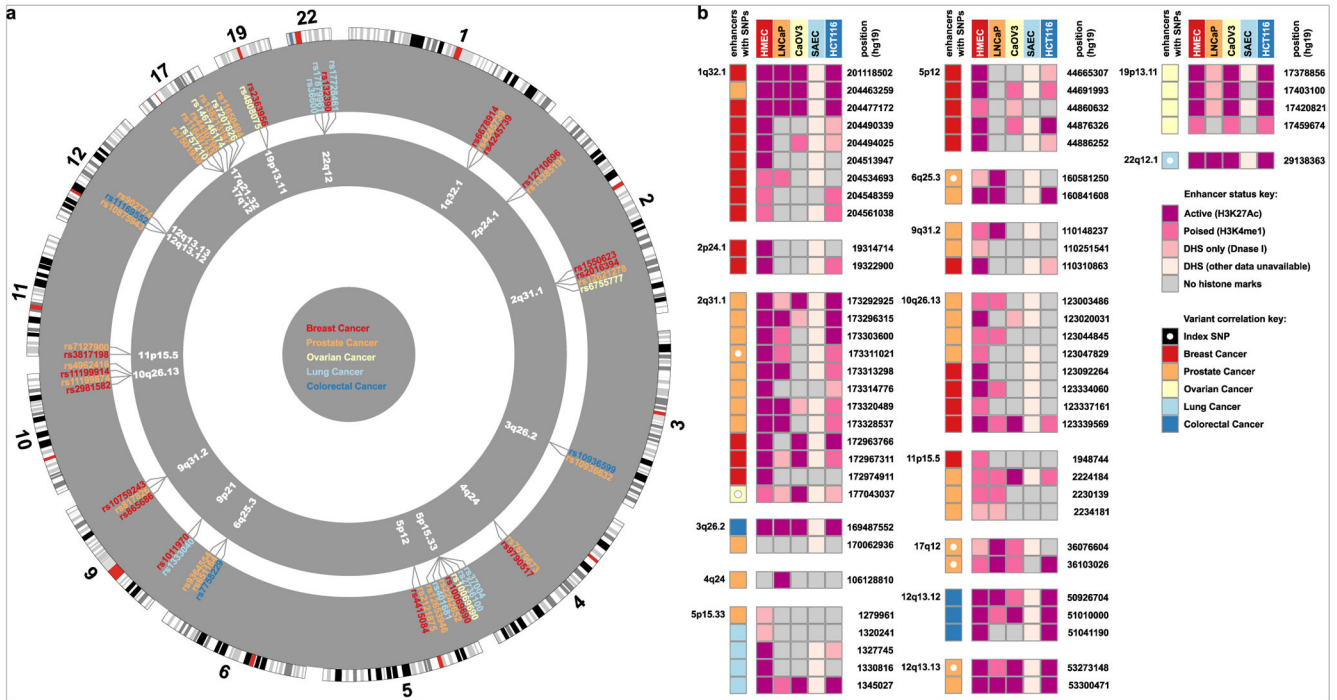
Figure 1.
Twenty risk regions analyzed as part of the GAME-ON OncoArray, including 17 pleiotropic regions conferring risks to two or more common cancers (breast, colorectal, lung, ovarian or prostate cancers). Panel (a) – Circos plot illustrating the 24 different regions ordered by chromosome and cytoband. The index SNP(s) at each locus are color coded by cancer type, (b) integration of correlated risk SNPs at each locus with regional catalogues of regulatory marks for related tissue types for common cancers to identify SNPs intersecting tissue specific regulatory targets. Publically available genome wide regulatory profiling data were available for the HMEC mammary epithelial cells (specific to breast cancer), LNCap cancer cells (for prostate cancer), CaOV3 cancers (for ovarian cancer), SAEC cells (for lung cancer). The first column indicates a risk-associated SNP that intersects a regulatory mark, color coded by cancer type. For other columns, colored squares represent an intersection between a risk associated SNP and a regulatory mark, and in which tissue type, indicating which marks are common across tissues and which are tissue specific. White squares indicate the most strongly associated SNPs (index SNP) in a region and a dot within the square indicates an intersection between a regulatory mark and an index. The position of each regulatory mark is indicated relative to hg19 coordinates. In panel b, only SNPs with regulatory marks are shown, thus excluding 24 of the regional associations shown in panel a.
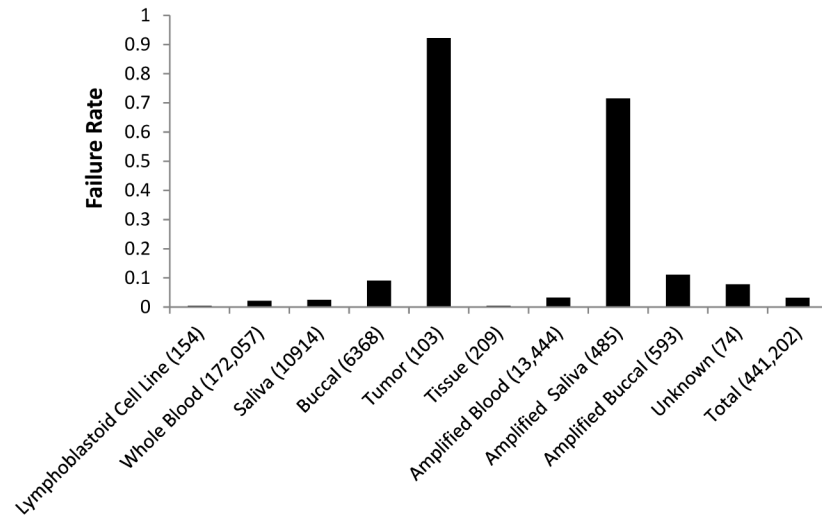
Figure 2.
Failure rates (<95% of SNPs called) for 211,594 samples genotyped by CIDR across multiple tissue types. The overall failure rate was 2.97%.
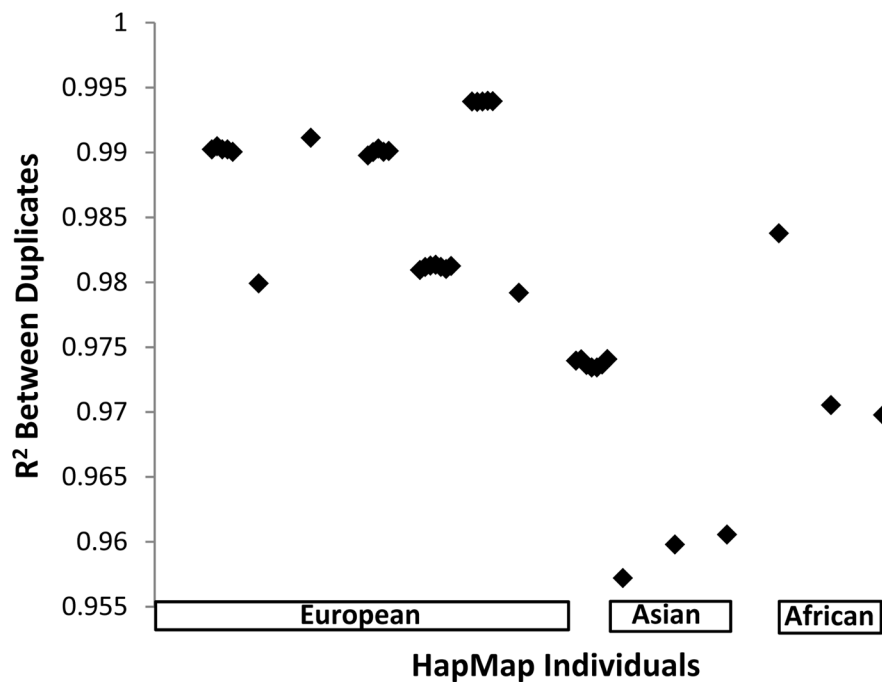
Figure 3.
Correlation between replicate Hapmap samples genotyped at Cambridge versus the Center
for Inherited Disease Research. Samples 1–8 are of European origin while samples 9–14 are
Asian or African. There are multiple replicates of samples 1, 4, 5, 6 and 8. Samples 1–8 are
European, 9–10 are Chinese, sample 11 is Japanese and samples 12–14 are Yoruban.

Table 1

Organization of SNP requests within consortia

Selection of SNP	Consortium				
	TRICL	BCAC/DRIVE/CIMBA	FOCI/OCAC	ELLIPSE/PRACTICAL	CORECT
Fine Mapping	0.437	0.259	0.700	0.359	0.346
Significant SNPs from Existing GWAS	0.032	0.465	0	0.379	0.598
Sequencing/Rare Variants	0.001	0.075	0	0.025	0.012
Other GWAS Studies/Ethnicities	0.072	0.044	0	0.128	0.005
Candidate SNP and Pathways	0.156	0.012	0.105	0.056	0.027
Correlated Phenotypes	0.083	0.015	0	0.051	0
GxG or GxE Interactions	0.004	0.063	0.115	0	0.012
SNPs from Tumor Genes	0.053	0	0	0	0
Functional and eQTL	0.161	0.005	0.002	0	0
Survival	0	0.062	0.079	0	0
SNPs within consortium	32,464	88,475	42,921	67,757	37,397