Uniform Survey of Allele-Specific Binding and Expression Across 383 Individuals

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Abstract

Large-scale sequencing of personal genomes has revealed multitudes of genomic variants, but for the majority, their functional impact is unknown. Here, we provide functional annotation for many variants, including rare ones, using allele-specific behavior, which can be assessed by observing allelic imbalance in the readouts of ChIP-seq and RNA-seq experiments. To this end, we pool and uniformly re-process many previous experiments, organizing the results into a database, AlleleDB. Overall, we detect 169,235 allele-specific binding SNVs and 144,083 allele-specific expression SNVs, representing 41% and 21% of SNVs accessible to the respective assays. Using the accessible non-allelic SNVs as a control, we identify genomic annotations (genes and categories of non-coding elements) significantly enriched or depleted in allele-specific behavior, such as the SNURF and FHIT genes and promoters with binding sites for RPB2 and PU.1 transcription factors. Finally, we find that allele-specific SNVs tend to be in regions under less purifying selection.

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Introduction

In recent years, the number of personal genomes has increased dramatically, from single individuals[1–3] to large sequencing projects such as the 1000 Genomes Project[4], UK10K[5] and the Personal Genome Project[6]. These efforts have provided the scientific community with a massive catalog of human genetic variants, most of which are rare.[4] Subsequently, a major challenge is to functionally annotate all of these variants.

Much of the characterization of variants so far has been focused on those found mainly in the protein-coding regions, but the advent of large-scale functional genomic assays, such as chromatin immunoprecipitation sequencing (ChIP-seq) and RNA sequencing (RNA-seq), has facilitated the annotation of genome-wide variation. This can be accomplished by correlating some form of functional readouts from the assays to genomic variants, particularly in identifying regulatory variants, such as mapping of expression quantitative trait loci (eQTLs)[7–9] and allele-specific (AS)[10,11] variants. eQTL mapping assesses the effects of variants on expression profiles across a large population of individuals and is usually used for detection of common regulatory variants. On the other hand, AS approaches assess phenotypic differences directly at heterozygous loci within a single genome. Using each allele in a diploid genome as a perfectly matched control for the other allele, AS variants can be detected regardless of their allele frequencies. Therefore, AS approaches are very useful, in terms of functionally annotating personal genomes, for identifying cis-regulatory variants on a large scale.

Early high throughput implementations of AS approaches employed microarray technologies, and thus are restricted to a subset of loci.[12–14] Later studies have used ChIP-seq and RNA-seq experiments for genome-wide scans of AS variants but have been mostly limited to a single assay with a variety of individuals,[15] or a few individuals with deeply-sequenced and well-annotated genomes.[11,16] For instance, GM12878, a very well-characterized lymphoblastoid cell-line from a Caucasian female, has several RNA-seq datasets and a huge trove of ChIP-seq data of more than 50 transcription factors (TFs) distributed in more than one study.[17–19] Merging these datasets is advantageous, be it increasing statistical power or simply having more features for more intra- and inter-individual comparisons (such as TFs and populations).

AS variant detection is extremely sensitive to the technical issues of variant calling and RNA-seq and ChIP-seq experiments, such as heterozygous variant calling and read mapping.[20–23] For example, reads mapping to copy number variants can be erroneously regarded as regions of allelic imbalance, resulting in AS variants being falsely detected. Moreover, studies with the appropriate datasets are typically designed for various purposes, resulting in disparate sets of computational tools, strategies and threshold parameters used in the processing of data in each respective study.[24,25] These reasons portend that simply pooling results from multiple studies may not be optimal even for the same biological sample. The task of merging has to be carried out in a uniform and meaningful manner to yield interpretable results. To this end, we organize and unify datasets from eight different studies into a comprehensive data corpus and repurpose it specifically for allele-specific analyses. We detect more than 169K and 144K single nucleotide variants (SNVs) associated with allele-specific binding (ASB) and expression (ASE) events respectively. We are able to present a systematic survey of these detected AS SNVs in various categories of coding and non-coding genomic annotations. The variants and annotations are

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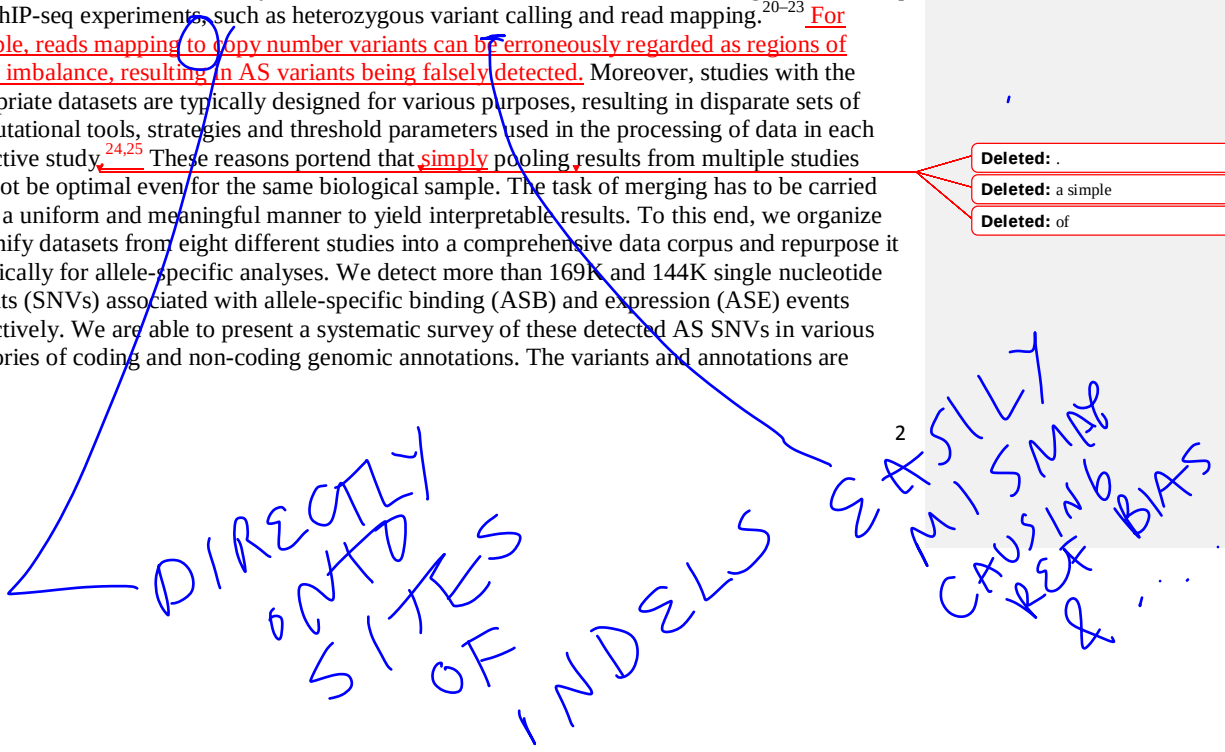

available in a resource, AlleleDB (http://alleledb.gersteinlab.org/). Finally, using our consolidated data, we investigate the extent of purifying selection in allele-specific SNVs and the inheritance of allele-specific binding in seven different transcription factors.

Results

Workflow and AlleleDB

There are two layers of information with respect to an individual that needs to be integrated in order to more accurately detect AS SNVs: (1) the DNA sequence of the individual, and (2) reads from either the RNA-seq or ChIP-seq experiment to look for SNVs associated with ASB or ASE. Here, we implement a uniform pipeline to combine personal genomic, transcriptomic and binding data and to standardize our detection of potential AS SNVs (Figure 1). First, we construct a diploid personal genome for each of the 383 individuals, using variants from the 1000 Genomes Project. Next, we pool the reads from each individual's ChIP-seq or RNA-seq and align them to each of the haploid genome. In total, we reprocess 142 ChIP-seq and 475 RNA-seq datasets for 383 individuals. Lastly, the AS SNVs are detected based on allelic imbalance of reads between the two haplotypes at heterozygous loci. For ChIP-seq data, the SNVs are additionally pared down to those within peak regions (see Methods).

We further define sets of 'control' SNVs. This is especially pertinent to our enrichment analyses, since the results are dependent on the choice of the null expectation (controls). The control SNVs are not allele-specific and are derived from a set of 'accessible' SNVs, which are heterozygous SNVs and possess at least the minimum number of reads to be statistically detectable for allelic imbalance. The accessible SNVs are determined for each ChIP-seq (grouped by individual and TF, not by study) or RNA-seq dataset (Table 1). In other words, these controls match the AS SNVs by statistical accessibility and being heterozygous.

By comparing AS SNVs relative to the control SNVs in each genomic annotation (see Methods), we investigate the enrichment (or depletion) of AS SNVs in 953 categories of non-coding genomic elements, including DNaseI hypersensitivity sites and transcription factor binding motifs from ENCODE Integrative release[26], and 20,144 protein-coding genes from GENCODE[27]. Additionally, this analysis is also extended to gene elements, such as introns and promoter regions and six other gene categories, including housekeeping and imprinted genes (Figure 2, see Methods). Together, these provide a systematic survey of ASB and ASE with respect to various functional annotations in the human genome.

We build a database, AlleleDB (http://alleledb.gersteinlab.org/), to house the annotations, and the candidate AS and accessible SNVs. AlleleDB can be downloaded as flat files or queried and visualized directly as a UCSC track in the UCSC Genome browser[28] as specific genes or genomic locations. This enables cross-referencing of AS variants with other track-based datasets and analyses, and makes it amenable to all functionalities of the UCSC Genome browser. Heterozygous SNVs found in the stipulated query genomic region are color-coded (AS SNVs are red, accessible SNVs are black) in the displayed track.

Allele-specific variants and enrichment analyses

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Of great interest, is the annotation of these allele-specific SNVs with respect to known genomic elements, both coding and non-coding. Using the AlleleDB variants found in the personal genomes of the 2 parents of the trio and 380 unrelated individuals from Phase 1 of the 1000 Genomes Project, we focus on autosomal SNVs and found that ~56% of our candidate ASE SNVs and ~6% of ASB SNVs are in coding DNA sequences (CDS). Overall, we detected 144,083 ASB and 169,235 ASE SNVs, representing 22% and 41% of the accessible SNVs respectively (Table 1). Further, for ASB SNVs, we observed statistical significance ($p < 0.05$) for 787 non-coding categories and 15 protein-coding genes and for ASE SNVs, 598 non-coding categories and 831 genes, with varying degree of enrichment and depletion of AS SNVs (Supp file). Table 2 shows the top 10 genes and non-coding regions enriched in AS SNVs.¶
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Using the AlleleDB variants found in the personal genomes of the 2 parents of the trio and 380 unrelated individuals from Phase 1 of the 1000 Genomes Project, we focus on autosomal SNVs and detected 144,083 ASE and 169,235 ASB SNVs, representing 21% and 41% of the accessible SNVs respectively (Table 1). The higher number of ASB SNVs observed is in line with a previous study that showed more variability in binding than in expression among individuals.[19] Of great interest, is the annotation of these AS SNVs with respect to known genomic elements, both coding and non-coding. ~56% of our candidate ASE SNVs and ~6% of ASB SNVs are in the coding DNA sequences (CDS). From 953 non-coding categories, we observed statistical significance (Bonferoni-corrected $p < 0.05$) for 716 and 467 categories for ASB and ASE SNVs respectively. From 20,144 protein-coding genes, we observed statistical significance for 31 and 442 genes for ASB and ASE SNVs respectively (supp file). For example, SNURF is a maternally-imprinted gene significantly enriched in allele-specific behavior in our analyses. It has shown to be highly implicated in the Prader-Willi Syndrome, an imprinting disorder.[29] On the other hand, FHIT is a tumor suppressor gene significantly depleted in allele-specific behavior, known to be implicated in a variety of cancers and appears to be a sensitive locus with high occurrence of loss-of-heterozygosity and hypermethylation.[30,31]

Figure 2 shows the enrichment of AS SNVs to provide a survey of AS regulation in elements closely related to a gene model, namely enhancers, promoters, CDS, introns and untranslated regions (UTR). In general, both categories of AS SNVs are more likely found in the 5' and 3' UTRs, suggesting allele-specific regulatory roles in these regions. On the other hand, intronic regions seem to exhibit a dearth of allele-specific regulation. For SNVs associated with allele-specific expression (ASE), a greater enrichment in 3' UTR than 5' UTR regions might be, in part, a result of known RNA-seq bias.[32,33] For SNVs associated with allele-specific binding (ASB), we also observe an enrichment in the promoters, hinting at functional roles in these variants found in TF binding motifs or peaks found near transcription start sites in the promoter regions to regulate gene expression. However, we see variable enrichments of ASB SNVs of particular TFs in promoter regions such as RPB2, while depletion in others, such as PU.1 (Figure 2, Supp file). These differences imply that some TFs are more likely to participate in allele-specific regulation than others.

We also compute the enrichment of AS SNVs in various gene categories. Some of them have been known to be involved in monoallelic expression (MAE), namely imprinted genes,[34] and three sets of genes known to undergo allelic exclusion: olfactory receptor genes,[35] immunoglobulin,[36] genes associated with T cell receptors and the major histocompatibility complex.[37] Monoallelic exclusion is a process exhibiting monoallelic expression, whereby one allele is being expressed while the other is silenced or repressed.[38,39] We also include a list of genes found to experience random monoallelic expression (RME) in a study by Gimelbrant *et al* (2007).[40] As expected, most of the MAE gene sets have been found to be significantly enriched in both ASB and ASE SNVs, with the exception of the olfactory receptor and RME genes. Interestingly, while a statistically significant enrichment of ASB SNVs is observed in the constitutively expressed housekeeping genes, there is no enrichment in ASE SNVs (Figure 2).

Rare variants and purifying selection in AS SNVs

To assess the occurrence of ASB and ASB SNVs in the human population, we consider the population minor allele frequencies (MAF). Table 1 shows the breakdown of the accessible and

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AS SNVs in seven ethnic populations and allele frequencies. Yoruba from Ibadan, Nigeria (YRI) contributes the most to both ASE and ASB variants at each allele frequency category. The number of rare AS SNVs (MAF≤ 0.5%) is about two folds higher in the YRI (~48% ASE SNVs and ~34% ASB SNVs with MAF≤ 5%) than the other European sub-populations of comparable (CEU, FIN) or larger (TSI) population sizes. In general, rare variants do not form the majority of all the AS variants. Nonetheless, we observe a shift towards very low allele frequencies in AS SNVs, peaking at MAF≤ 0.5% (Figure 3).

To examine selective constraints in AS SNVs, we consider the enrichment of rare variants with MAF≤ 0.5%.[4,41] Our results show lower enrichment of rare variants in AS SNVs as compared to non-AS SNVs. This posits that, as a whole, AS SNVs are under lesser selective constraints than non-AS SNVs. Such weaker selection may be a result of accommodating varying degrees of gene expression across individuals. In addition, ASB SNVs seem to be under lesser selective constraints than ASE SNVs, which aligns with more variability being observed.

ASB Inheritance analyses using CEU trio

The CEU trio is a well-studied family and particularly, many ChIP-seq studies were performed on different TFs. Previous studies have presented AS inheritance in a few TFs as a case-study.[11,18] Here, we provide a more comprehensive and statistical investigation of the heritability of ASB (Figure 4 and Supp file). For the DNA-binding protein CTCF, we observe a high parent-child correlation (Figure 4), denoting great similarity in allelic directionality (slope of regression line, β=0.86 in both parent-child plots). High inheritance of AS SNVs with the same allelic direction from parent to child implies a sequence dependency in allele-specific behavior. Besides CTCF, PU.1, SA1, PAX5 and POL2 also show AS inheritance. On the contrary, MYC and RPB2 exhibit β< 0.5, indicating that AS inheritance is not as apparent in some TFs – inheritance of AS behavior may not be a universal phenomenon.

Discussion

Much research on regulatory variants has been performed using eQTL mapping of common variants. AS analyses can provide a complementary approach to detect regulatory variants. Firstly, we found a substantial number of very rare AS SNVs with MAF≤ 0.5%. This group of SNVs is harder to access by eQTL mapping and the number is expected to increase with more personal genomes. Secondly, in eQTL mapping, correlation is drawn between total expression measured between individuals in a population and their genotypes. This is allele-insensitive as the total expression across a locus is measured. As such, effects from trans-factors such as negative feedback mechanism that sought to reduce total expression variance across individual genomes with different genotypes will not be detected. However, in an AS approach, even if the total expression is the same across genotypes, difference in allelic expression can still be detected. Such a within-individual control in an AS approach also eliminates normalization issues across multiple assays. Thirdly, eQTL mapping is contingent on population size for sufficient statistics, while the AS approach can detect AS effects *en masse* within a single individual's genome. This makes it an attractive strategy for biological samples such as primary cells and tissues that are difficult to obtain in large numbers.

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An AS approach is able to detect many AS SNVs for a single personal genome. But as we increase the number of personal genomes, we see that the number of private or rare variants accumulates as well and many of them might be involved in regulation. Thus, it is important to increase the number of personal genomes, ChIP-seq and RNA-seq datasets by capitalizing on existing ones, motivating the development of a pipeline that can uniformly process a large number of personal genomic data for AS detection.

Our analyses place an emphasis on relating allele-specific activity to known genomic annotations, such as CDS and various non-coding regions, and many diseases have been found to implicate ASE in particular genomic regions.[43–45] Therefore, our analyses can help to characterize genomic variants on two levels: firstly, at the single nucleotide level, where our detected AS SNVs can serve as an annotation to variant catalogs (e.g. 1000 Genomes Project) in terms of allele-specific cis-regulation; secondly, by associating AS SNVs with a genomic annotation, we might be able to define categories of genomic regions more attuned to allele-specific activity. Additionally, we can provide some further insights by associating ASB of TFs with ASE of genes, by comparing the ASB and ASE enrichments within the same category of genomic region. For example, the high enrichment of AS SNVs in most loci associated with monoallelic expression can imply coordination of ASE events by ASB. The exceptions are the groups of RME and olfactory receptor genes, where another mechanism (besides ASB) might be causing ASE in these genes. This can help to prioritize downstream experimental characterization to determine if such allele-specific binding (evidenced by ChIP-seq experiments) do exist and if so, whether it leads to any phenotypic differences.[46]

However, there are still concerns about diversity of samples. Firstly, our current catalog of AS SNVs is detected from lymphoblastoid cell lines (LCLs), which is the predominant cell-line type in the literature. However, it has already been known that there is considerable variability in regulation of gene expression in different tissues.[47] Data from projects, such as ENCODE[36] and GTEx[47], which has more functional assays and sequencing in other tissues and cell lines can be incorporated to provide a more wholesome AS analysis. Secondly, our search for datasets shows a dearth of personal genomes with corresponding ChIP-seq and RNA-seq data in non-European and non-African populations. It could be a strong reflection on the lack of large-scale functional genomics assays in specific ethnic groups – a concern echoed previously in population genetics and is recently being increasingly addressed.[48] Since many AS variants have been found to be rare at both the individual and the sub-population level, it is of great interest and importance that more individuals of diverse ancestries be represented.

In conclusion, we have shown that there is great value and utility in pooling existing data, and it has to be processed in a uniform fashion to eliminate issues of heterogeneity in various standards and parameters etc. More accurate allelic information is also being achieved with the advent of longer reads to help in haplotype reconstruction and phasing in next-generation sequencing.[49–51] As technology evolves and more diverse personal genomes and functional genomics data become available, AlleleDB is intended as a scalable resource to accommodate new individual genomes, tissue and cell types. Such should be especially valuable, not only for researchers interested in allele-specific regulation but also for the scientific community at large.

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Materials and Methods

AlleleDB

The final data and results are organized into a resource, AlleleDB (http://alleledb.gersteinlab.org/), which conveniently interfaces with the UCSC genome browser for query and visualization. Since many in the scientific community are familiar with the genome browser, we hope that this would increase the accessibility and usability of AlleleDB. The query results are also available for download in the BED format, which is compatible with other tools, such as the Integrated Genome Viewer[52]. More in-depth analyses can be performed by downloading the full set of AS results. For ASB, the output will be delineated by the sample ID and the associated TFs; for ASE, the output will be categorized by individual and the associated gene. We also provide the raw counts for each accessible SNV and indicate if it is identified as an AS SNV. AlleleDB also serves as an annotation of allele-specific regulation of the 1000 Genomes Project SNV catalog.

Genomic annotations

Categories of gene elements from Figure 2, such as promoters, CDS regions and UTRs, and 20,144 protein-coding gene annotations (HGNC symbols) are obtained from GENCODE version 17.[27] Promoter regions are set as 2.5kbp upstream of all transcripts annotated by GENCODE.

Gene annotations also ~~include~~ 2.5kbp upstream of the start of gene. 953 categories of non-coding annotations are obtained from ENCODE Integrative release,[26] which includes broad categories such as TF binding sites and more specific annotations such as distal binding sites of particular TFs, e.g. ZNF274. Note that these TF binding sites are separate from those sites in promoter regions in Figure 2, which are based on the 58 TFs and peaks from the ChIP-seq experiments used in our pipeline.

Genes for random monoallelic expression are from Gimelbrant *et. al*. (2007)[40] The olfactory receptor gene list is from the HORDE database[35]; immunoglobulin, T cell receptor and MHC gene lists are from IMGT database[36]. We performed enrichment analyses on a number of enhancer lists, which are derived using the ChromHMM and Segway algorithms (Ernst and Kellis (2012)[53], Hoffman *et. al*. (2013)[54]), and data from distal regulatory modules from Yip *et al*. (2012)[55]. The result for the enhancers in Figure 2 is based on the union of these lists. The lists can be found at http://info.gersteinlab.org/Encode-enhancers. An additional enhancer list for experimentally validated enhancers is obtained from VISTA enhancer browser database[56] (http://enhancer.lbl.gov/). Housekeeping gene list is obtained from Eisenberg and Levanon (2013) (http://www.tau.ac.il/~elieis/HKG/)[57].

All enrichment analyses results with respect to these annotations are provided in the supplementary files.

Construction of diploid personal genomes

There are a total of 383 genomes used in this study: 380 unrelated genomes, of low-coverage (average depth of 2.2 to 24.8) from Utah residents in the United States with Northern and Western European ancestry (CEU), Han Chinese from Beijing, China (CHB), Finnish from Finland (FIN), British in England and Scotland (GBR), Japanese from Tokyo, Japan (JPT),

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Toscani from Italy (TSI), and Yorubans from Ibadan, Nigeria (YRI) and 3 high-coverage genomes from the CEU trio family (average read depth of 30x from Broad Institute's, GATK Best Practices v3; variants are called by UnifiedGenotyper). Each diploid personal genome is constructed from the SNVs and short indels (both autosomal and sex chromosomes) of the corresponding individual found in the 1000 Genomes Project. This is constructed using the tool, *vcf2diploid*.[16] Essentially, each variant (SNV or indel) found in the individual's genome is incorporated into the human reference genome, hg19. Most of the heterozygous variants are phased in the 1000 Genomes Project; those that are not, are randomly phased. As a result, two haploid genomes for each individual are constructed. When this is applied to the family of CEU trio, for each child's genome, these haploid genomes become the maternal and paternal genomes, since the parental genotypes are known. Subsequently, at a heterozygous locus in the child's genome, if at least one of the parents has a homozygous genotype, the parental allele can be known. However, for each of the genomes of the 380 unrelated individuals, the alleles, though phased, are of unknown parental origin.

CNV genotyping is also performed for each genome by CNVnator,[58] which calculates the average read depth within a defined window size, normalized to the genomic average for the region of the same length. For each low coverage genome, a window size of 1000 bp is used, while for the high coverage genomes, a window size of 100 bp is used. SNVs found within genomic regions with a normalized abnormal read depth <0.5 or >1.5 are filtered out, since these would mostly likely give rise to spurious AS detection.

RNA-seq and ChIP-seq datasets

RNA-seq datasets are obtained from the following sources: gEUVADIS[15], ENCODE[26], Lalonde *et al.* (2011)[59], Montgomery *et al.* (2010)[60], Pickrell *et al.* (2010)[7], Kilpinen *et al.* (2013)[18] and Kasowski *et al.* (2013)[19].

ChIP-seq datasets are obtained from the following sources: ENCODE[26], McVicker *et al.* (2013)[61], Kilpinen *et al.* (2013)[18] and Kasowski *et al.* (2013)[19].

Allele-specific SNV detection

AS SNV detection is performed by AlleleSeq.[16] For each ChIP-seq or RNA-seq dataset, reads are aligned against each of the derived haploid genome (maternal/paternal genome for trio) using Bowtie 1.[62] No multi-mapping is allowed and only a maximum of 2 mismatches per alignment is permitted. Sets of mapped reads from various datasets are merged into a single set for allele counting at each heterozygous locus. Here, a binomial p-value is derived by assuming a null probability of 0.5 sampling each allele. To correct for multiple hypothesis testing, FDR is calculated. Since statistical inference of allele-specificity of a locus is dependent on the number of reads of the ChIP-seq or RNA-seq dataset, this is performed using an explicit computational simulation.[16] Briefly, for each iteration of the simulation, a mapped read is randomly assigned to either allele at each heterozygous SNV and performs a binomial test. At a given p-value threshold, the FDR can be computed as the ratio of the number of false positives (from the simulation) and the number of observed positives. An FDR cutoff of 10% is used for ChIP-seq data and 5% for RNA-seq data, since the latter is typically of deeper coverage. Furthermore, we allow only significant AS SNVs to have a minimum of 6 reads. For ChIP-seq data, AS SNVs have to be also within peaks. Peak regions are provided as per those called from each publication

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of origin, except for the dataset from McVicker *et al*. (2013), in which there are no peak calls. In the latter case, we determine the peaks by performing PeakSeq[63] using the unmapped control reads provided by McVicker *et al*. (2013) via personal communication with the author. We use PeakSeq version 1.2 with default parameters and mapability map for human genome (hg19) to call peaks. The peaks that pass q-value threshold of 0.05 are marked as significant and used in the analyses.

Enrichment analyses

Accessible SNVs, in addition to being heterozygous, also exceed the minimum number of reads detectable statistically by the binomial test. This is an additional criterion imposed, besides the minimum threshold of 6 reads used in the AlleleSeq pipeline. The minimum number of reads varies with the pooled size (coverage) of the ChIP-seq or RNA-seq dataset. Given a fixed FDR cutoff, for a larger dataset, the binomial p-value threshold is typically lower, making the minimum number of reads (N) that will produce the corresponding p-value, larger. This alleviates a bias in the enrichment test for including SNVs that do not have sufficient reads in the first place. Considering an extreme allelic imbalance case where all the reads are found on one allele (all successes or all failures), this minimum N can be obtained from a table of expected two-tailed binomial probability density function, such that accessible SNVs are all SNVs with number of reads, n = max(6,N). The control (non-AS) ASB or ASE SNVs are accessible SNVs excluding the respective ASB or ASE SNVs. Enrichment analyses are performed using the Fisher's exact test. P-values are Bonferroni-corrected and considered significant if < 0.05.

AS inheritance analyses

We compute the allelic ratio as the proportion of reads that align to the reference allele with respect to the total number of reads mapped to either allele of a particular site, for each parent-child pair. Since AS events can only be detected at heterozygous sites, we consider all SNVs shared by parent and child from two scenarios: (1) when an AS SNV is heterozygous in all three individuals but common to the two individuals being compared, and (2) when an AS SNV is heterozygous in two individuals and homozygous (reference or alternate) in the third. We then calculate the slope using regression analysis, with the parent's allelic ratio as the independent variable (X) and the child's as the dependent variable (Y): $Y = \beta X + \alpha$. Pearson's correlation coefficients (r) are also provided in the supplementary table. For the parent-parent comparison, the maternal allelic ratio is chosen arbitrarily to be the independent variable; the correlation coefficient might be a better measure in this case.

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Acknowledgements

The authors would like to thank Dr. Rob Bjornson for technical help.

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Figure caption

Figure 1. Workflow for uniform processing of data from 383 individuals and construction of AlleleDB. For each of the 383 individuals, a diploid personal genome is first constructed using the variants from the 1000 Genomes Project. Next, reads from ChIP-seq or RNA-seq data are mapped onto each of the haploid genome of the diploid genome. At each heterozygous SNV, a comparison is made between the number of reads that map to either allele, and a statistical significance (after multiple hypothesis test correction) is computed to determine if a SNV is allele-specific (AS). All the candidate AS variants are then deposited in AlleleDB database. Additional information, such as raw read counts of both accessible non-AS and AS variants, can be downloaded for further analyses.

Figure 2. Some genomic regions are more inclined to allele-specific regulation. We map variants associated with allele-specific binding (ASB; green) and expression (ASE; blue) to various categories of genomic annotations, such as coding DNA sequences (CDS), untranslated regions (UTRs), enhancer and promoter regions, to survey the human genome for regions more enriched in allelic behavior. Using the accessible non-AS SNVs as the expectation, we compute the log odds ratio of ASB and ASE SNVs individually, via Fisher's exact tests. The number of asterisks depicts the degree of significance (Bonferonni-corrected): *, p<0.05; **, p<0.01; ***, p<0.001. For each transcription factor (TF) in AlleleDB, we also calculate the log odds ratio of ASB SNVs in promoters, providing a proxy of allele-specific regulatory role for each available TF. Genes known to be monoallelically expressed such as imprinted and MHC genes (CDS regions) are highly enriched for both ASB and ASE SNVs. The actual log odds ratio of T cell receptor genes for ASE SNVs and MHC genes for ASB and ASE SNVs are indicated on the bars.

Figure 3. A considerable fraction of AS variants are rare but do not form the majority. Lesser proportion of AS SNVs than non-AS SNVs are rare, suggesting lesser selective constraints in AS SNVs. The minor allele frequency (MAF) spectra of ASB (green filled circle), accessible non-ASB SNVs (green open circle), ASE (blue filled circle) and accessible non-ASE SNVs (blue open circle) are plotted at a bin size of 100. The peaks are in the bin for MAF < 0.5%.The inset zooms in on the histogram at MAF < 3%. Comparing ASE+ to ASE- gives an odds ratio of 0.67 (hypergeometric p < 2.2e-16), while comparing ASB+ to ASB-, gives an odds ratio of 0.96 (p=0.0021), signifying statistically significant depletion of AS variants relative to non-AS variants in both cases. This depletion suggests that AS SNVs are under less purifying selection.

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Figure 4. Inheritance of allele-specific binding events is evident in some TFs but not so apparent in others. The left panel shows plots for the TFs CTCF (top row) and MYC (bottom row) being examined for inheritance in the CEU trio (Father: NA12891, Mother: NA12892, Daughter: NA12878). Each point on the plot represents the allelic ratio of a common ASB SNV between the parent (x-axis; blue) and the child (y-axis; green), by computing the proportion of reads mapping to the reference allele at that SNV. The correlation is evaluated by the slope of the regression, β. High β values in CTCF in both parent-child comparisons signify strong heritability in allele-specific behavior. On the other hand, MYC shows low β values, suggesting that AS inheritance is not apparent. The table at the top right panel presents the β values for all seven TFs used in our analyses, in descending order of heritability.

Table 1.
Table 1 shows the breakdown of SNVs in each ethnic population: heterozygous (HET), accessible (ACC) and ASE SNVs in Table 1A and ASB SNVs in Table 1B. For each of the last 3 columns, each category of HET, ACC and AS SNVs is further stratified by the minor allele frequencies: common (MAF > 0.05), rare (MAF ≤ 0.01) and very rare (MAF ≤ 0.005). The number of AS SNVs is given as a percentage of the ACC SNVs. Table 1 also provides the number of individuals from each ethnic population with RNA-seq and ChIP-seq data available for the ASE and ASB analyses respectively.

Supplementary Figures

Supplementary Table 1
This table shows the slope and Pearman's correlation results for all seven DNA-binding proteins for parent-child and parent-parent comparisons. CTCF, PU.1, SA1, PAX5 and POL2 exhibit AS inheritance but MYC and RPB2 do not seem to have very apparent AS inheritance.

Supplementary Figures

Supplementary File 1
This Excel file contains results from our AS analyses for 953 categories from ENCODE, including the Fisher's exact test odds ratios, p-values (original and Bonferroni-corrected), the number of AS SNVs and accessible non-AS SNVs found in each category. The results for 5 gene element categories from GENCODE and 16 enhancer categories are also included. 'NA' is marked in categories where odds ratio cannot be calculated due to insufficient numbers in non-AS SNVs. These are tabulated for ASB, ASE and AS, which is the combined unique number of ASB and ASE SNVs.

Supplementary File 2
This Excel file contains results from our AS analyses for the 20,144 protein-coding genes (HGNC symbols) from GENCODE, including the Fisher's exact test odds ratios, p-values (original, Bonferroni-corrected), the number of AS SNVs and accessible non-AS SNVs found in the gene region. The results for housekeeping genes and 5 monoallelically-expressed gene categories are also included. 'NA' is marked in categories where odds ratio cannot be calculated

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Supplementary File 3

This Excel file contains the ASB enrichment in promoter regions for 58 TFs used in our database, including the Fisher's exact test odds ratios, p-values (original, Bonferroni-corrected), the number of ASB SNVs, accessible non-AS SNVs both found and not found in the gene region. ASB SNVs for each TF are contributed by different individuals. If either of the parents in the CEU trio is involved, ASB SNVs for NA12878 are not included. Those TFs with only ASB SNVs from NA12878 are annotated '1' under the column 'NA12878 only'. 'NA' is marked in categories where odds ratio cannot be calculated due to insufficient numbers in any of the last three columns.

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