

Potential etiologic and functional implications of genome-wide association loci for human diseases and traits

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We have developed an online catalog of SNP-trait associations from published genome-wide association studies for use in investigating genomic characteristics of trait/disease-associated SNPs (TASs). Reported TASs were common [median risk allele frequency 36%, interquartile range (IQR) 21%–53%] and were associated with modest effect sizes [median odds ratio (OR) 1.33, IQR 1.20–1.61]. Among 20 genomic annotation sets, reported TASs were significantly overrepresented only in nonsynonymous sites [OR = 3.9 (2.2–7.0), $p = 3.5 \times 10^{-7}$] and 5kb-promoter regions [OR = 2.3 (1.5–3.6), $p = 3 \times 10^{-4}$] compared to SNPs randomly selected from genotyping arrays. Although 88% of TASs were intronic (45%) or intergenic (43%), TASs were not overrepresented in introns and were significantly depleted in intergenic regions [OR = 0.44 (0.34–0.58), $p = 2.0 \times 10^{-9}$]. Only slightly more TASs than expected by chance were predicted to be in regions under positive selection [OR = 1.3 (0.8–2.1), $p = 0.2$]. This new online resource, together with bioinformatic predictions of the underlying functionality at trait/disease-associated loci, is well-suited to guide future investigations of the role of common variants in complex disease etiology.

catalog | evolution | GWAS | polymorphism | disorders

In the past 3 years, genome-wide association studies (GWAS) assaying hundreds of thousands of SNPs in thousands of individuals have reproducibly identified hundreds of associations of common genetic variants with over 80 diseases and traits (<http://www.genome.gov/gwastudies>). These studies have progressed from assaying fewer than 100,000 SNPs to more than one million, and sample sizes have increased dramatically as the search for variants that explain more of the disease/trait heritability has intensified (1). Important insights from these studies thus far include generally small effect sizes (odds ratios often <1.5), putative risk loci in or near genes not previously suspected of being involved in the etiology of a particular disease/trait, associated loci in common among diseases not previously thought to share etiologic pathways, and associations in many chromosomal regions currently annotated as gene poor (1).

The rapid increase in the number of GWAS provides an unprecedented opportunity to examine the potential impact of common genetic variants on complex diseases by systematically cataloging and summarizing key characteristics of the observed associations and the trait/disease associated SNPs (TASs) underlying them. Although some of these aspects have been examined on a smaller scale for individual diseases such as type 2 diabetes (2), inflammatory bowel disease (3), and cancer (4), a comprehensive genome-wide analysis across all GWAS published to date has not been conducted.

Identifying published GWAS can be challenging. For example, a simple PubMed search using the words “genome wide association studies” produced over 2,000 citations through December 2008, most of which are not actual GWAS. With this in mind, we developed the manually curated National Human Genome

Research Institute (NHGRI) Catalog of Published Genome-Wide Association Studies (<http://www.genome.gov/gwastudies>), an online, regularly updated database of SNP-trait associations extracted from published GWAS. Here, we (i) describe the features of this resource and the methods we have used to produce it, (ii) provide and examine key descriptive characteristics of reported TASs such as estimated risk allele frequencies and odds ratios, (iii) examine the underlying functionality of reported risk loci by mapping them to genomic annotation sets and assessing overrepresentation via Monte Carlo simulations and (iv) investigate the relationship between recent human evolution and human disease phenotypes. There are several challenges in conducting these analyses within the present context wherein the actual functional variant is often unknown. Specifically, for a given TAS, the causative variant may be: (i) the TAS itself, (ii) a known common SNP in strong linkage disequilibrium (LD) with the TAS, (iii) an unknown common SNP or rare single nucleotide variant tagged by a haplotype on which the TAS occurs, or (iv) a linked copy number variant. Due to the limited annotation for categories (iii) and (iv), our analyses focus on the role of reported TASs and their LD partners (TASPs) only. Further, the power of analyses to detect overrepresentation of causative variants in specific functional categories may be weakened by the need to consider all of the TASPs within the LD block tagged by a TAS (we will refer to this as a TAS block). To circumvent this issue we use a strategy that calculates the overrepresentation of unique TAS blocks in specific categories (i.e., for a particular category, a TAS block is counted once if one or more unique member TASPs map to the category) rather than individual TASPs (*Methods*).

Results

Descriptive and Association Data. We examined associations from a total of 151 (of 237) published GWAS (through December, 2008) reporting at least one TAS at $p < 5 \times 10^{-8}$ ([supporting information \(SI\) Table S1](#)). Including replication sample sizes reported in 130 (86%) of these 151 studies, the median total sample size for initial + replication studies was 7,858 participants (range, 146–91,749). From the 151 studies, we extracted information on 531 SNP-trait associations (limiting to one TAS per gene region and trait, as described in *SI Text*).

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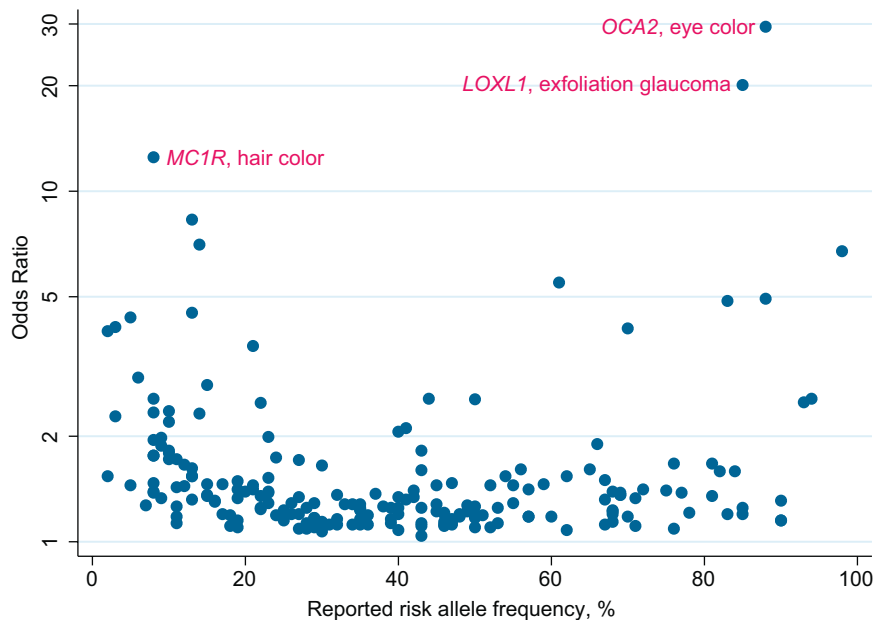


Fig. 1. Published odds ratios for discrete traits by reported risk allele frequencies. Labeled SNP-trait associations are those with the highest ORs. Note that the y axis is on the log scale.

Unsurprisingly, since the GWAS method is primarily powered for common alleles, risk allele frequencies were well above 5% (median risk allele frequency 36%, interquartile range, IQR, 21%–53%) in the populations analyzed as well as in the HapMap populations (CEU: 37%, 21–54%; YRI: 33%, 13–65%; combined JPT+CHB 32%, 13–58%; Fig. S1).

The 531 reported SNP-trait associations represented 465 unique TASs; 43% ($n = 199$) of which were located in an intergenic region, 45% ($n = 208$) were intronic, 9% ($n = 41$) were nonsynonymous, 2% ($n = 10$) were in a 5' or 3' untranslated region, and 2% ($n = 7$) were synonymous, according to the University of California Santa Cruz Genome Browser (5). Discrete traits were the focus of 227 (43%) of the 531 SNP-trait associations, which had associated odds ratios (ORs) ranging from 1.04 to 29.4 (median 1.33, IQR 1.20–1.61; Fig. S2). Among the discrete traits, the range of ORs was similar between nonsynonymous and other TASs; however, the right tail of the OR distribution for nonsynonymous TASs was slightly skewed toward higher values. The highest ORs were reported for pigmentation traits [Fig. 1; *MC1R* and hair color (6) and *OCA2* and eye color (6)]. SNP-trait associations were also distributed widely across diseases of high population prevalence, including heart disease, obesity, diabetes, and cancer (Table S2). Trait prevalence was not associated with the magnitude of ORs and risk allele frequencies, which were similar between the 10 most prevalent traits and all others combined (median ORs 1.26 and 1.29, respectively; median risk allele frequencies, 40% and 35%, respectively).

Among genes or regions harboring TASs that were reported in multiple studies of discrete traits, 18 were associated with seemingly distinct traits that may suggest clues toward common etiologic pathways (Table 1). Several TASs were located in previously characterized candidate genes, such as *APOE*, *HLA*, *KCNJ11*, *PPARG*, and *CARD15*, and were detected through GWAS at comparable effect sizes and stronger levels of statistical significance (Table S3). In these instances, GWAS-identified SNPs served as reasonable positive controls for known disease-associated genetic variants.

Functional Analysis. To assess the underlying functionality at the trait/disease-associated genetic loci, we systematically mapped

all TASPs (reported index TASs with an association p value $< 5.0 \times 10^{-8}$ and all HapMap phase II CEU SNPs in LD [$r^2 > 0.9$]) to 20 nonmutually exclusive genomic annotation sets (Table S4). For each annotation set, we did the following. For every unique TAS block, we determined whether any TASPs mapped to the annotation set. If none mapped, we did not count the block. However, if one or more TASPs mapped, then we counted 1 per block. To compute the odds of a TAS block mapping to the annotation set, we divided the number of unique TAS blocks that were counted in the annotation set (n) by the number of TAS blocks that were not counted ($N-n$). To evaluate whether any annotation set was significantly enriched or depleted for TAS blocks, we compared the observed odds with the expected odds calculated from 100 control datasets comprised of randomly selected SNPs and their LD partners. Importantly, the mapping and counting strategies were consistent across both the test and the control datasets to ensure a fair comparison. Further, the generation of the control datasets took into account the representation biases on the genotyping arrays that were used to identify the TASs (SI Text).

For 9 annotation sets (nonsynonymous sites, 1kb promoters, 5kb promoters, most conserved sequences (MCSs), 3' UTRs, microRNA target sites, Introns, CpG islands and experimentally validated regulatory regions from ORegAnno), the 95% confidence interval (CI) of the OR excluded 1.0 and the enrichment p values were < 0.05 (Fig. S3), indicating that these categories may be significantly enriched for TAS blocks. Nonsynonymous sites had the strongest signal for enrichment (OR = 3.9 [2.2–7.0], $p = 3.5 \times 10^{-7}$). After restricting the analysis to only those nonsynonymous SNPs predicted by PolyPhen (7) to be potentially deleterious (which reduces the sample size by approximately 65%), TAS blocks were even more strongly enriched (OR = 5.2 [1.8–15.3], $p = 0.001$). Thirty nonsynonymous TASPs that are predicted to be potentially deleterious [by PolyPhen and an unpublished method, CDPred (P. Cherukuri and J. Mullikin, personal communication)] were identified as attractive candidates for functional follow-up (Table 2).

To examine the possibility that signals in other annotation sets might not represent bona fide TAS block enrichment, but rather a “hitchhiking” effect whereby TASPs closely linked with non-

Table 1. Reported TASs associated with two or more distinct traits

Chromosomal region	Rs number(s)	Attributed genes	Associated traits reported in catalog
1p13.2	rs2476601, rs6679677	<i>PTPN22</i>	Crohn's disease, type 1 diabetes, rheumatoid arthritis
1q23.2	rs2251746, rs2494250	<i>FCER1A</i>	Serum IgE levels, select biomarker traits (MCP1)
2p15	rs1186868, rs1427407	<i>BCL11A</i>	Fetal hemoglobin, F-cell distribution
2p23.3	rs780094	<i>GCKR</i>	CRP, lipids, waist circumference
6p21.33	rs3131379, rs3117582	<i>HLA / MHC region</i>	Systemic lupus erythematosus, lung cancer, psoriasis, inflammatory bowel disease, ulcerative colitis, celiac disease, rheumatoid arthritis, juvenile idiopathic arthritis, multiple sclerosis, type 1 diabetes
6p22.3	rs6908425, rs7756992, rs7754840, rs10946398, rs6931514	<i>CDKAL1</i>	Crohn's disease, type 2 diabetes
6p25.3	rs1540771, rs12203592, rs872071	<i>IRF4</i>	Freckles, hair color, chronic lymphocytic leukemia
6q23.3	rs5029939, rs10499194	<i>TNFAIP3</i>	Systemic lupus erythematosus, rheumatoid arthritis
7p15.1	rs1635852, rs864745	<i>JAZF1</i>	Height, type 2 diabetes*
8q24.21	rs6983267	<i>Intergenic</i>	Prostate or colorectal cancer, breast cancer
9p21.3	rs10811661, rs1333040, rs10811661, rs10757278, rs1333049	<i>CDKN2A, CDKN2B</i>	Type 2 diabetes, intracranial aneurysm, myocardial infarction
9q34.2	rs505922, rs507666, rs657152	<i>ABO</i>	Protein quantitative trait loci (TNF- α), soluble ICAM-1, plasma levels of liver enzymes (alkaline phosphatase)
12q24	rs1169313, rs7310409, rs1169310, rs2650000	<i>HNF1A</i>	Plasma levels of liver enzyme (GGT), C-reactive protein, LDL cholesterol
16q12.2	rs8050136, rs9930506, rs6499640, rs9939609, rs1121980	<i>FTO</i>	Type 2 diabetes, body mass index or weight
17q12	rs7216389, rs2872507	<i>ORMDL3</i>	Asthma, Crohn's disease
17q12	rs4430796	<i>TCF2</i>	Prostate cancer, type 2 diabetes
18p11.21	rs2542151	<i>PTPN2</i>	Type 1 diabetes, Crohn's disease
19q13.32	rs4420638	<i>APOE, APOC1, APOC4</i>	Alzheimer's disease, lipids

* The well known association of JAZF1 with prostate cancer was reported with a p value of 2×10^{-6} (18), which did not meet the threshold of 5×10^{-8} for this analysis.

synonymous SNPs map to nearby annotation sets and artificially increase their ORs, we removed all TASP blocks having $r^2 > 0.6$ with any nonsynonymous HapMap CEU SNP and repeated the test (Fig. 2). Only 2 categories retained a clear signal for enrichment—1-kb promoters (OR = 3.0 [1.4 – 6.5], $p = 0.005$) and 5-kb promoters (OR = 2.3 [1.5 – 3.6], $p = 0.0003$). After Bonferroni correction for 20 comparisons, only the enrichment signal from 5-kb promoters remained significant, although this may reflect greater power relative to 1-kb promoters due to a larger number of mapped TASP blocks. Although no other category had even an uncorrected enrichment p value < 0.05 , a few showed nonsignificant trends toward enrichment, such as the ORegAnno elements (OR = 2.0 [0.95 – 4.4], $p = 0.09$). We note here that the number of TAS blocks mapping to 1kb promoter regions was similar to or smaller than several other categories (Table S4), so power is unlikely to explain the strong enrichment signal in promoter regions and lack thereof elsewhere.

Using previous predictions of high confidence transcription factor binding sites in human 1-kb promoter regions, 4 TASP blocks were predicted to have strong allele-specific TF binding affinities (Table S5). These predictions may lead to compelling hypotheses for trait/disease etiology, as in the case of the protective allele [G] of SNP rs1077834, which is predicted to abolish a partially conserved binding site for HNF4 α 696 base pairs upstream of the *LIPC* transcription start site. HNF4 α is an essential hepatic transcriptional activator that has been associated with metabolic pathways (8) and has been shown to activate *LIPC*, an important enzyme in lipid metabolism (9). One could thus hypothesize that the loss of HNF4 α binding in the presence of the protective allele may lower *LIPC* expression, leading to increased plasma HDL levels.

Intergenic regions, despite harboring the largest fraction of TAS blocks, were significantly depleted for TAS blocks (OR = 0.44 [0.34 – 0.58], $p = 2.0 \times 10^{-9}$). This is consistent with the assumption that intergenic regions, although containing important regulatory sequences, have the smallest ratio of functional to total DNA. Intronic regions and several putative functional categories within intergenic regions (such as predicted intergenic transcription factor binding sites, experimentally supported enhancer regions, noncoding RNAs, and regions of conserved RNA secondary structures) did not show evidence for enrichment or depletion (Fig. 2). However, a definitive interpretation of this result is hindered by the current lack of extensive experimental annotation and noisy computational predictions of functional elements within intergenic regions.

Although conservation across species is a popular proxy for important functionality, enrichment analysis in the mammalian Most Conserved Sequences (MCSs) revealed no TAS block enrichment signal (OR = 1.07 [0.75 – 1.5], $p = 0.79$). However, ORegAnno sites—experimentally supported regulatory elements of which many are nonconserved—did show a trend toward TAS block enrichment (Fig. 2; OR = 2.0 [0.95–4.4], $p = 0.09$). This affirms the need for more experimental investigation into the architecture of noncoding regulatory elements (such as enhancers and microRNAs) to decrease the reliance on conservation and guide more integrative computational prediction methodologies.

To ensure the robustness of our results, we repeated the analyses using different r^2 thresholds for defining LD partners ($r^2 = 1.0$ and $r^2 > 0.8$) and the results were essentially unchanged (data not shown). Although even lower r^2 thresholds are reasonable for capturing more of the possible causative variants,

Table 2. Predicted deleterious non-synonymous TASP s with $p < 5 \times 10^{-8}$. Sixteen nonsynonymous trait/disease associated SNPs and their strong linkage disequilibrium partners (TASP s defined here as $r^2 > 0.9$), are predicted to be deleterious according to both PolyPhen (PP) and CDPred (CDP), 7 only by PP and 7 only by CDP

Non-synonymous TASP	Amino acid change	Index TAS from GWAS	Affected gene	Reported gene	Trait/disease	Program
rs1046934	Q59H	rs2274432	<i>TSEN15</i>	<i>GLT25S2</i>	Height	PP & CDP
rs2305479	G282R	rs7216389	<i>GSDMB</i>	<i>ORMDL3</i>	Asthma	PP & CDP
rs2305480	P289S	rs2872507	<i>GSDMB</i>	<i>ORMDL3</i>	Crohn's disease	PP & CDP
rs3197999	R689C	rs3197999	<i>MST1</i>	<i>MST1</i>	Crohn's disease	PP & CDP
rs2476601	R620W	rs2476601	<i>PTPN22</i>	<i>PTPN22</i>	Rheumatoid arthritis	PP & CDP
rs2395029	V112G	rs2395029	<i>HLA-C</i>	<i>HLA-C</i>	Psoriasis	PP & CDP
rs4149056	V174A	rs4149056	<i>SLCO1B1</i>	<i>SLCO1B1</i>	Myopathy	PP & CDP
rs7578597	T1187A	rs7578597	<i>THADA</i>	<i>THADA</i>	T2D	PP & CDP
rs229527	G21V	rs229541	<i>C1QTNF6</i>	<i>C1QTNF6</i>	T1D	PP & CDP
rs11820589	P148L	rs12272004	<i>BUD13</i>	<i>APOA</i>	LDL/TG	PP & CDP
rs676210	P2739L	rs673548	<i>APOB</i>	<i>APOB</i>	Metabolic traits	PP & CDP
rs1799990	M129V	rs1799990	<i>PRNP</i>	<i>PRNP</i>	Creutzfeldt-Jacob disease	PP & CDP
rs6756629	R50C	rs6756629	<i>ABCG5</i>	<i>ABCG5</i>	LDL	PP & CDP
rs1800562	C282Y	rs1800562	<i>HFE</i>	<i>HFE</i>	Serum markers of iron status	PP & CDP
rs328	Nonsense	rs10503669	<i>LPL</i>	<i>LPL</i>	HDL/TG	PP & CDP
rs601338	Nonsense	rs492602	<i>FUT2</i>	<i>FUT2</i>	Vitamin B12	PP & CDP
rs2274432	G19D	rs2274432	<i>TSEN15</i>	<i>GLT25D2</i>	Height	PP only
rs11591147	R46L	rs11591147	<i>PCSK9</i>	<i>PCSK9</i>	LDL	PP only
rs11887534	D19H	rs11887534	<i>ABCG8</i>	<i>ABCG8</i>	Gallstones	PP only
rs1799969	G241R	rs1799969	<i>ICAM1</i>	<i>ICAM1</i>	Soluble ICAM1	PP only
rs17467284	R911L	rs11175593	Predicted	<i>LRRK2 / MUC19</i>	Crohn's disease	PP only
rs1260326	P446L	rs1260326	<i>GCKR</i>	<i>GCKR</i>	TG	PP only
rs1064608	P290A	rs10838738	<i>MTCH2</i>	<i>MTCH2</i>	BMI	PP only
rs1042602	S192Y	rs1042602	<i>TYR</i>	<i>TYR</i>	Freckles	CDP only
rs6046	R413Q	rs561241	<i>Factor VII</i>	<i>Factor VII</i>	Factor VII level	CDP only
rs16969968	D398N	rs8034191	<i>CHRNA5</i>	<i>CHRNA5</i>	Lung cancer	CDP only
rs16890979	V282I	rs16890979	<i>SLC2A9</i>	<i>SLC2A9</i>	Serum uric acid	CDP only
rs2231142	Q141K	rs2231142	<i>ABCG2</i>	<i>ABCG2</i>	Serum uric acid	CDP only
rs3761472	D110G	rs2281135	<i>SAMM50</i>	<i>SAMM50</i>	Plasma level of liver enzymes	CDP only
rs1169288	I27L	rs2650000	<i>HNF1A</i>	<i>HNF1A</i>	LDL	CDP only

they will also likely pick up a greater number of irrelevant variants that will only obscure the interpretation. When we repeated the analysis using a threshold of $r^2 > 0.6$, results for 4 categories changed substantially—CpG islands and ORegAnno elements displayed a stronger enrichment signal and introns and MCSs revealed a stronger signal for depletion.

Evolutionary Analysis. To assess evolutionary characteristics of TASS, we used the integrated haplotype score (iHS), which is a measure of recent positive selection designed to detect extended haplotypes due to selective sweeps (10). The proportion of TASS (not the full set of TASP s as we wanted to select only one SNP for each TAS block) with iHS above the 90th percentile (1.635) among HapMap Phase II CEU SNPs was slightly higher relative to background expectation (OR = 1.3 [0.8–2.1]), but only at $p = 0.2$. At least 50 TASS were predicted to be under positive selection (Table S6). Several risk alleles associated with melanin synthesis, immune response, and cancer were identified as having undergone recent moderate (iHS = 1.635–2.0) or strong (iHS > 2.0) positive selection (Table S6), consistent with previously established links between these traits/diseases and positive selection (11–13). Of particular interest are positively selected alleles that confer risk for obesity and related metabolic disorders (Table S6), because these are consistent with the long-standing thrifty gene hypothesis (14). Despite the popularity of this hypothesis, wherein genetic variants conferring resistance to starvation in hunter-gatherer populations were positively selected, a convincing “thrifty gene” has yet to be identified. The risk allele of rs1121980 in the fat mass and obesity

associated gene (*FTO*), which is involved in fat storage, has undergone recent positive selection by iHS analysis and is an attractive candidate for a thrifty gene.

Discussion

The availability of an online, curated, user-friendly, and downloadable catalog of GWAS and SNP-trait associations has facilitated a multifaceted analysis of published GWAS results. The more than 150 studies and 500 SNP-trait associations reviewed here demonstrate that, in general, reported TASS tend to be common (>5% minor allele frequency), are associated with modest effect sizes, and are not highly differentiated across populations. In addition, TAS blocks are significantly enriched in nonsynonymous sites (especially for potentially deleterious sites) and in promoter regions and are depleted in intergenic regions. Despite this enrichment, 43% of reported TASS were intergenic and 45% were intronic, suggesting a greater than anticipated role for noncoding SNPs in common diseases. The mere presence of a predicted deleterious nonsynonymous associated variant does not discount the possibility that a nearby SNP in LD may (i) be the true causative variant, (ii) confer an independent molecular mechanism for the phenotype, or (iii) epistatically interact with the nonsynonymous variant to cause disease. Despite the recent interest in the role of microRNA (miRNA) targeting dysfunction in human disease (15, 16), we found no evidence that predicted miRNA target sites in the 3' UTR were significantly enriched for TAS blocks (Fig. 2). Finally, predictions based on the integrated haplotype score (iHS) may

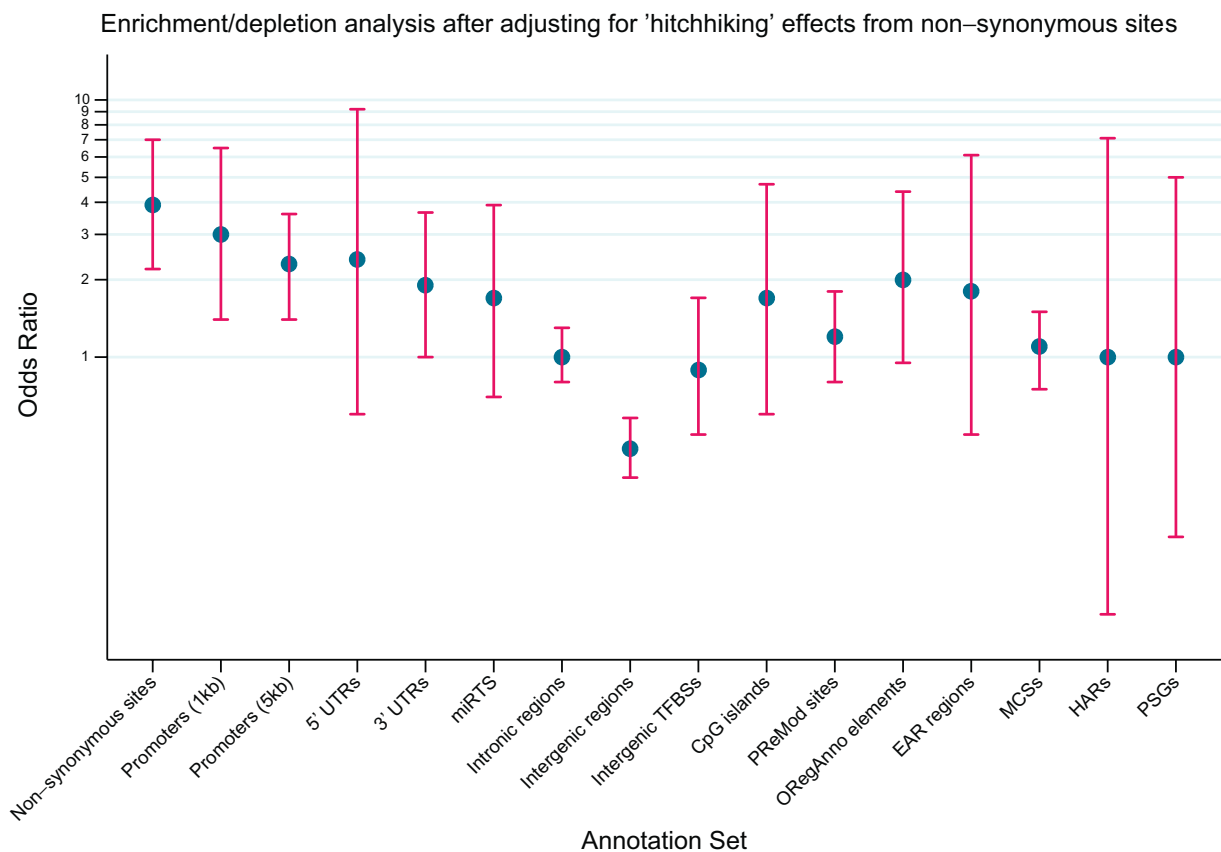


Fig. 2. Odds ratios for TAS block enrichment/depletion analysis after adjusting for “hitchhiking” effects from nonsynonymous sites. Four annotation sets (Splice sites, Validated enhancers, EvoFold elements, and noncoding RNAs) are not represented here because no TAS blocks mapped to these annotation sets. The blue circle represents the point estimate of the odds ratio (OR) and the red lines represent the 95% CI. Possible “hitchhiking” effects from nonsynonymous sites are reduced by discarding any TASP/control SNP in $r^2 > 0.6$ with a nonsynonymous SNP. For an explanation of the annotation sets on the x axis, we refer the reader to Table S4. Note that the y axis is on the log scale. Nonsynonymous OR computation is not adjusted for “hitchhiking” effects.

provide important clues about the evolutionary history and underlying molecular mechanisms of certain TASP.

Several limitations of the underlying catalog data should be noted. We extracted all eligible associations from published articles and *SI Text*, but the number and quality of reported SNP associations is dependent upon the preferences of the individual author and journal. Also, the studies within the catalog generally test only those SNPs that are detectable via commonly used genotyping platforms in participants who tend to be from European-descent populations. The GWAS data are likely to be subject to varying degrees of upward bias in effect size estimates (the “winner’s curse” phenomenon), particularly to the extent that estimates from the GWAS discovery population, who may be less representative of the general population, influence those reported in our catalog. Nonetheless, in several instances in which known candidate SNPs have been previously identified, GWAS of the same trait tended to confirm these findings with similar effect sizes and stronger levels of statistical significance. Finally, TASP reported in published GWAS suffer from “lead TAS bias”; generally 1 or 2 TASP out of a cluster are selected from the initial study, often based on likely functional significance such as a conserved nonsynonymous site, for association analysis in the replication sample. To minimize the effect of this bias, we analyzed TAS blocks, which include the lead SNPs and their known LD partners based on HapMap phase II data. However, the true impact of the bias is difficult to quantify and it may still exert a slight effect on the enrichment/depletion signals especially for categories such as nonsynonymous sites.

An important question is to what extent GWAS have identified genetic variants likely to be of clinical or public health importance, particularly for developing preventive or therapeutic interventions. Answering this question must await better functional characterization of TASP or the true causative variants they may be tagging, evidence of effective interventions, and identification of potential modifiers of SNP-trait associations (1). However, the current study contributes empiric bounds on the expectations for the effect sizes and allele frequencies of TASP that can be identified from GWAS. It also highlights the distribution of promising SNP-trait associations across a wide variety of traits of substantial public health interest, such as obesity, hypertension, coronary artery disease, and cancer. Our results may guide future studies by highlighting genetic variants that are of particular interest from a descriptive, association, evolutionary, or functional perspective (such as predictions of TASP-mediated allele-specific transcription factor binding sites) and suggesting hypotheses for future study. Our description of GWAS-identified variants builds upon the important work previously targeted toward candidate genes, adding to a more complete picture of the contribution of common genetic variation to common diseases. It is clear, however, that the proportion of heritability explained by common variation for most common diseases to date is modest at best (17). As the power of the GWAS approach increases with access to more samples, and as the types of methods to test for genetic associations expand to include copy number variants and rarer alleles, more associations will likely be identified and timely analyses similar to those presented here will continue to update our knowledge of the influence of genomic structure and function on complex diseases.

Methods

Catalog Development and Curation. Published GWAS were identified primarily through 2 sources: (i) weekly PubMed searches and (ii) daily NIH-distributed compilations of news and media reports. We also periodically consulted an online database of published genomic epidemiology literature (<http://www.cdc.gov/hugenet>). All studies assaying at least 100,000 SNPs in any subset of participants, typically referred to as the "initial scan," were included in the catalog, regardless of the number of SNPs that ultimately passed quality control and were used in analysis. Several study level and SNP-trait association level variables were extracted (*SI Text*). The somewhat liberal statistical threshold of $p < 1.0 \times 10^{-5}$ was chosen to allow examination of borderline associations and to accommodate scans of various sizes while maintaining a consistent approach. Filters on the catalog allow thresholding at various levels of p values or odds ratios. Additional detail about the catalog curation is available in the *SI Text*.

Descriptive and Association Analyses. We restricted these analyses to 151 of the 237 papers reporting a total of 531 SNP-trait associations with $p < 5 \times 10^{-8}$ through December 31, 2008, and corresponding to 465 unique SNPs. A com-

plete list of references and extracted catalog data for these analyses are available from the authors upon request. Statistical analyses were done in STATA Intercooled 8.0. Further details on the descriptive and association analyses are available in the *SI Text*.

Functional and Evolutionary Analyses. The 20 annotation sets were defined and obtained as described in *Table S4*. Each annotation set was assayed for enrichment or depletion as previously described (Results). Fisher's exact test p values were computed using the "Text::NSP::Measures::2D::Fisher" Perl module. Additional details of the functional and evolutionary analyses are provided in *SI Text*.

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1. Manolio TA, Brooks LD, Collins FS (2008) A HapMap harvest of insights into the genetics of common disease. *J Clin Invest* 118:1590–1605.
2. McCarthy MI, Hirschhorn JN (2008) Genome-wide association studies: Potential next steps on a genetic journey. *Hum Mol Genet* 17:R156–165.
3. Cho JH (2008) The genetics and immunopathogenesis of inflammatory bowel disease. *Nat Rev Immunol* 8:458–466.
4. Eeles RA, et al. (2008) Multiple newly identified loci associated with prostate cancer susceptibility. *Nat Genet* 40:316–321.
5. Kent WJ, et al. (2002) The human genome browser at UCSC. *Genome Res* 12:996–1006.
6. Sulem P, et al. (2007) Genetic determinants of hair, eye and skin pigmentation in Europeans. *Nat Genet* 39:1443–1452.
7. Ramensky V, Bork P, Sunyaev S (2002) Human nonsynonymous SNPs: Server and survey. *Nucleic Acids Res* 30:3894–3900.
8. Hayhurst GP, Lee YH, Lambert G, Ward JM, Gonzalez FJ (2001) Hepatocyte nuclear factor 4alpha (nuclear receptor 2A1) is essential for maintenance of hepatic gene expression and lipid homeostasis. *Mol Cell Biol* 21:1393–1403.
9. Rufibach LE, Duncan SA, Battle M, Deeb SS (2006) Transcriptional regulation of the human hepatic lipase (LIPC) gene promoter. *J Lipid Res* 47:1463–1477.
10. Voight BF, Kudaravalli S, Wen X, Pritchard JK (2006) A map of recent positive selection in the human genome. *PLoS Biol* 4:e72.
11. Summers K, Crespi B (2008) Molecular evolution of the prostate cancer susceptibility locus RNASEL: Evidence for positive selection. *Infect Genet Evol* 8:297–301.
12. Sabeti PC, et al. (2007) Genome-wide detection and characterization of positive selection in human populations. *Nature* 449:913–918.
13. Lao O, de Gruijter JM, van Duijn K, Navarro A, Kayser M (2007) Signatures of positive selection in genes associated with human skin pigmentation as revealed from analyses of single nucleotide polymorphisms. *Ann Hum Genet* 71:354–369.
14. Neel JV (1962) Diabetes mellitus: A "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet* 14:353–362.
15. Georges M, Coppieters W, Charlier C (2007) Polymorphic miRNA-mediated gene regulation: Contribution to phenotypic variation and disease. *Curr Opin Genet Dev* 17:166–176.
16. Sethupathy P, Collins FS (2008) MicroRNA target site polymorphisms and human disease. *Trends Genet* 24:489–497.
17. Visscher PM, Hill WG, Wray NR (2008) Heritability in the genomics era—concepts and misconceptions. *Nat Rev Genet* 9:255–266.
18. Thomas G, et al. (2008) Multiple loci identified in a genome-wide association study of prostate cancer. *Nat Genet* 40:310–315.