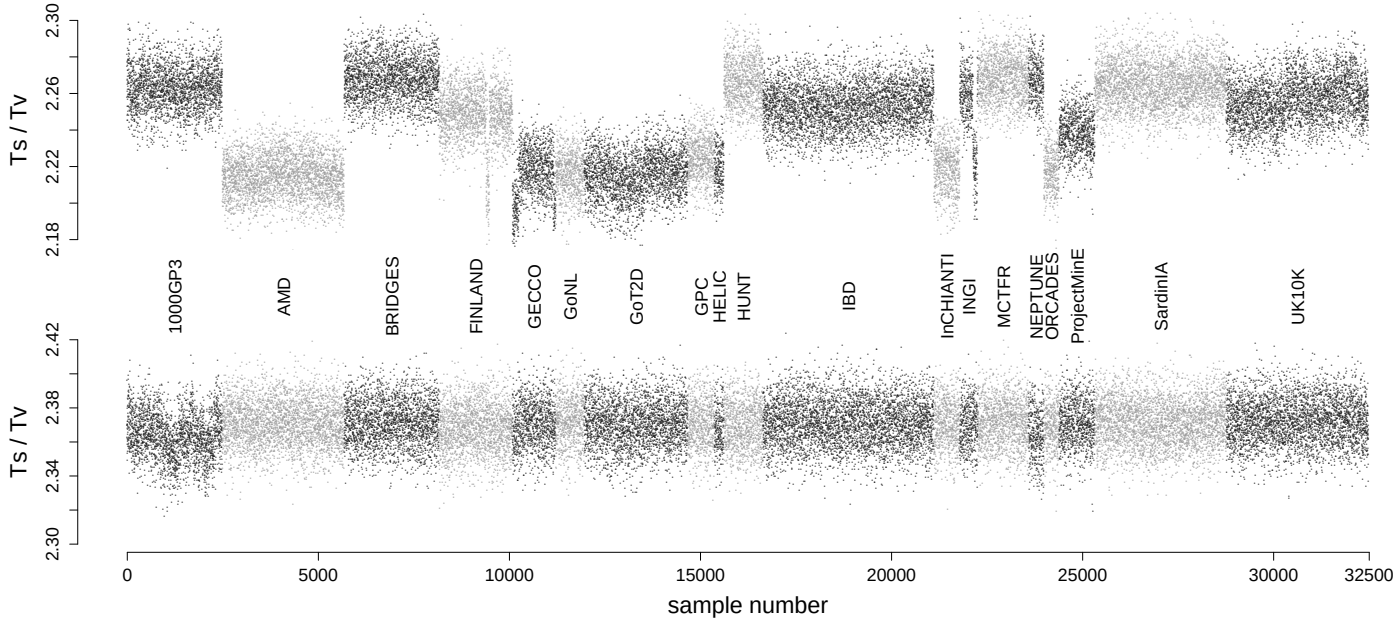
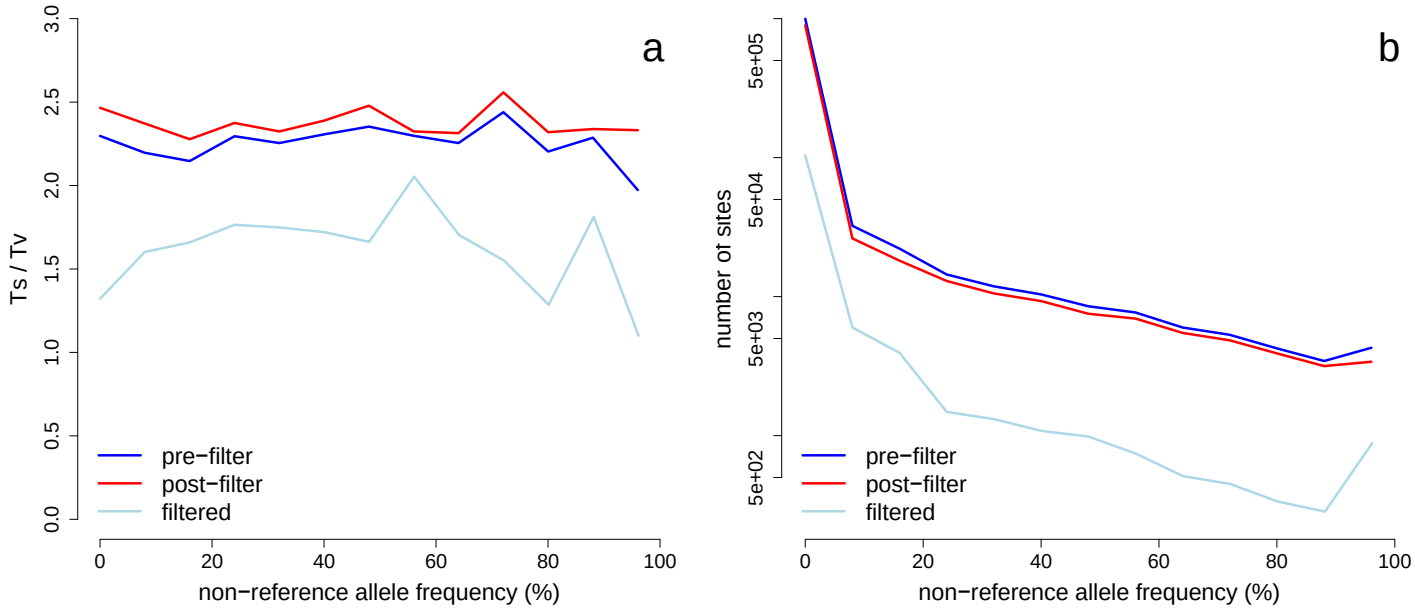


Supplementary Figure 1

The effect of sites filtering on Ts/Tv ratio per sample

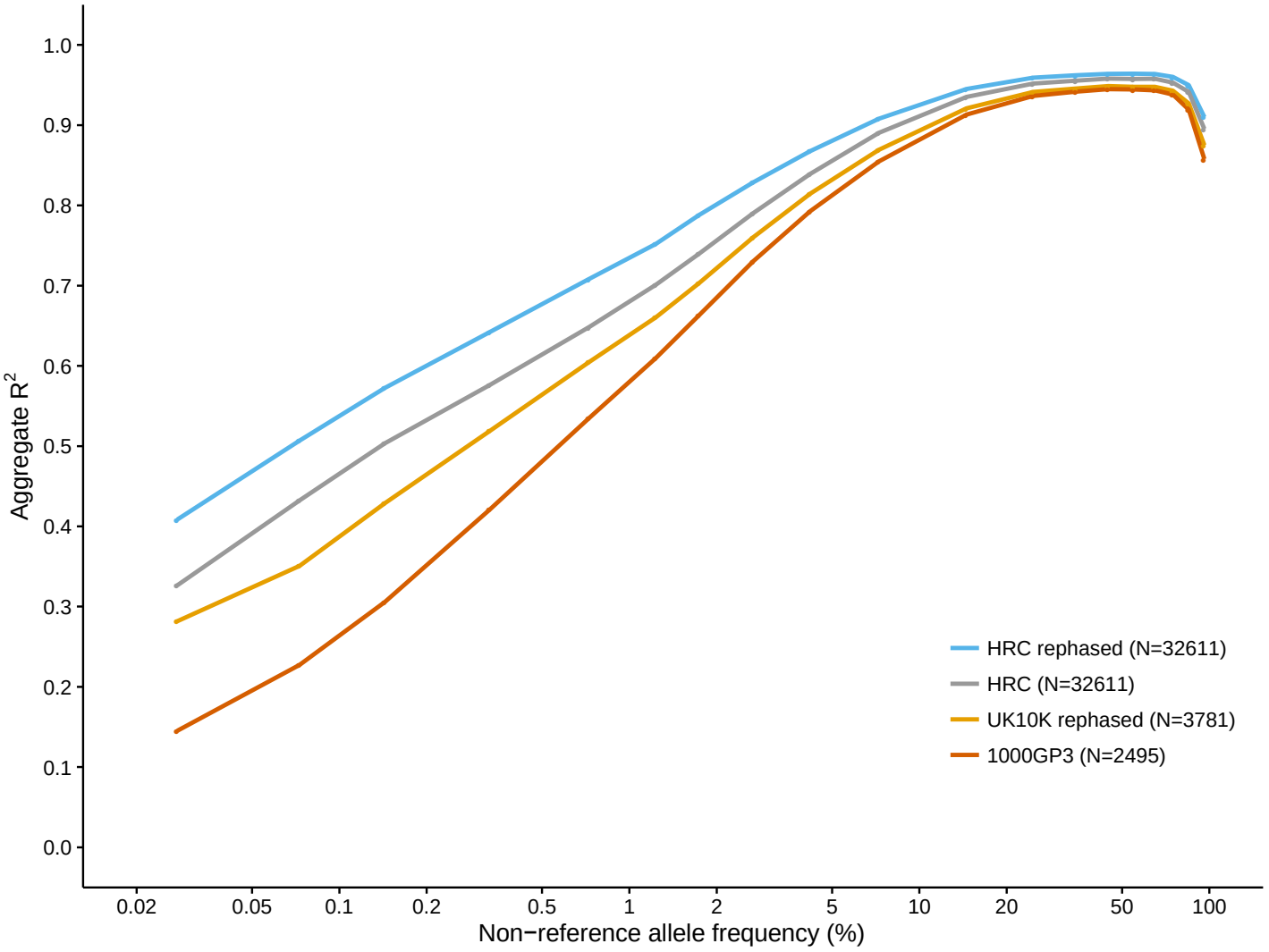
The top figure shows the per-sample transition-transversion ratio (Ts/Tv) for chromosome 20 after running the GLPhase genotype calling method on the full MAC5 site list. In the bottom figure, GLPhase was run after the site filtering described in the text.



Supplementary Figure 2

Data summaries before and after site filtering

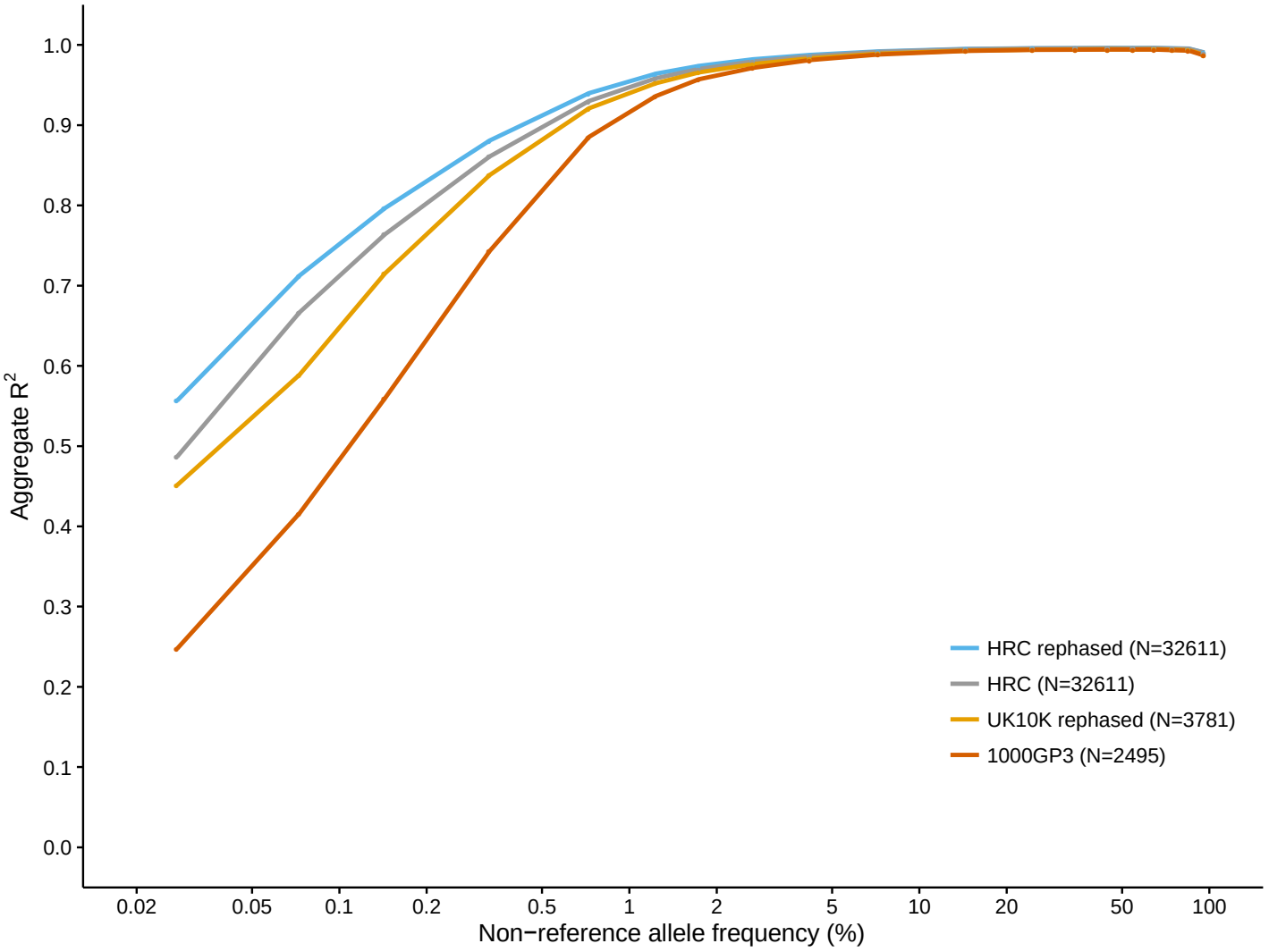
Figure a shows the number of sites in the unfiltered and filtered MAC5 site lists (chromosome 20) stratified by non-reference allele frequency. The allele frequency here is calculated from the genotypes made after running the GLPhase genotype calling method on the full MAC5 site list. Figure b shows the corresponding transition-transversion ratio (Ts/Tv) of these sites.



Supplementary Figure 3

Performance of imputation using different reference panels

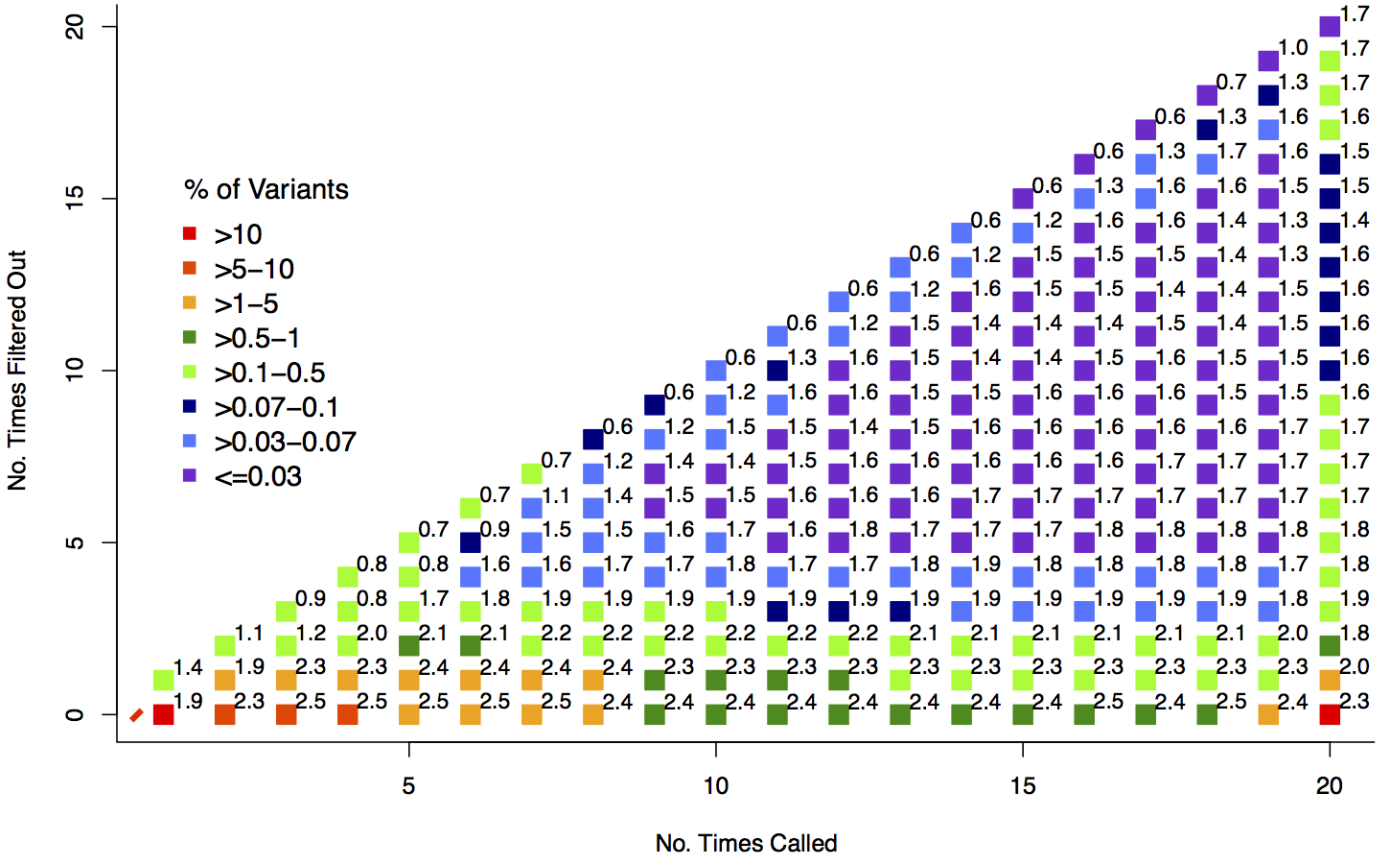
The x-axis shows the non-reference allele frequency of the SNP being imputed on a log scale. The y-axis shows imputation accuracy measured by aggregate r^2 when imputing SNP genotypes into 10 CEU samples. These results are based on using genotypes from sites on Illumina Core Exome SNP array.



Supplementary Figure 4

Performance of imputation using different reference panel.

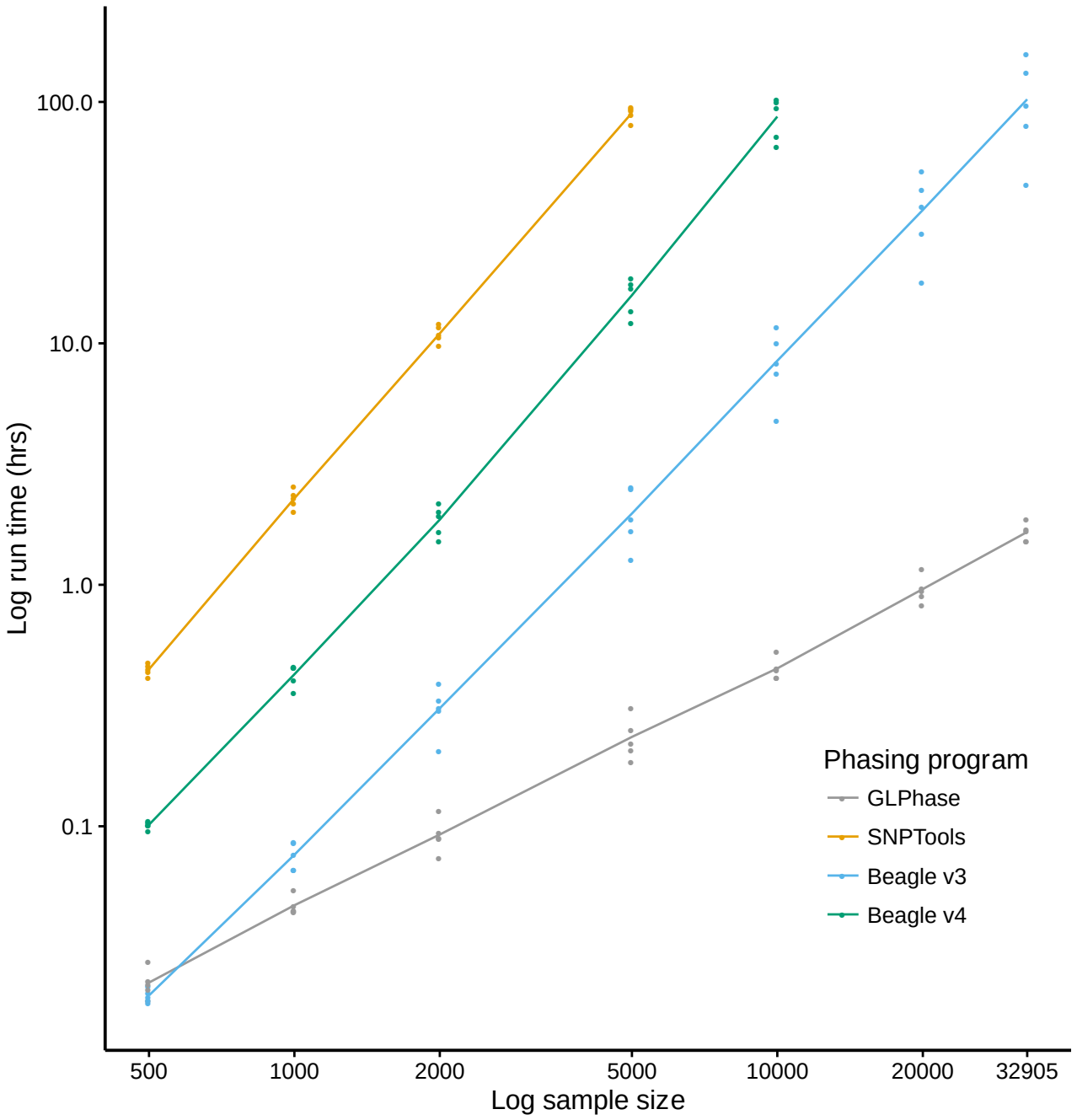
The x-axis shows the non-reference allele frequency of the SNP being imputed on a log scale. The y-axis shows imputation accuracy measured by aggregate r^2 when imputing SNP genotypes into 10 CEU samples. These results are based on using genotypes from sites on Illumina OMNI 5M SNP array.



Supplementary Figure 5

Site stratification by calling and filtering status across cohorts.

On the x-axis we show the number of studies a variant was called in (out of 20) and on the y-axis we show the number of times it was filtered out by the cohort-specific internal QC pipelines. The color shows the percentage of variants in each such cell (red means more than 10% of variants lie in that cell while blue means less than 0.1%). The number to the top right of each cell denotes the Ts/Tv ratio for all sites in that cell. Cells higher in the plot have been filtered out relatively often and usually represent poor variants, as is also seen from the low Ts/Tv ratio. All variants above the red line were filtered out (which excludes all cells which had been filtered independently by more than 4 studies or have Ts/Tv ratio less than 1.7)



Supplementary Figure 6

Comparison of methods for genotype calling as sample size increases

The figure shows a log-log plot of run time vs sample size for four different methods of genotype calling from GL data. For each sample size 5 random 1024 site chunks from chromosome 20 were used. Each dot represents the run time of a single dataset. Lines are drawn between successive means of run times for each value of sample size

Supplementary Tables

Cohort	# samples in Release 1	Depth	Website	Reference for cohort (where available)
UK10K	3715	6.5x	http://www.uk10k.org/	UK10K Consortium et al. The UK10K project identifies rare variants in health and disease. Nature (2015). doi:10.1038/nature14962
SardinIA	3445	4x	https://sardinia.irp.nia.nih.gov/	Sidore et al. Genome sequencing elucidates Sardinian genetic architecture and augments association analyses for lipid and blood inflammatory markers. Nat Genet. 2015 Nov;47(11):1272-81. doi: 10.1038/ng.3368.
IBD	4474	4x + 2x	http://www.ibdresearch.co.uk/	Barrett, J. C. et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat.

				Genet. 40, 955–962 (2008). Parkes et al. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. 39, 830–832 (2007).
GoT2D	2709	4x/Exome	http://www.type2diabetesgenetics.org/informational/got2d	Flannick, J. Whole-genome sequencing of 2,657 individuals and the genetic architecture of type 2 diabetes. *Nature* (in press)
BRIDGES	2487	6-8x (12x)		n/a
1000 Genomes Phase 3 (1000GP3)	2495	4x/Exome	http://www.1000genomes.org/	1000 Genomes Project Consortium et al. A global reference for human genetic variation. Nature 526, 68–74 (2015).
GoNL	748	12x	http://www.nlgenome.nl/	Genome of the Netherlands Consortium. Whole-genome sequence variation, population structure and demographic history of the Dutch population.

				Nat. Genet. 46, 818–825 (2014).
AMD	3189	4x		Chen W et al. Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. Proc Natl Acad Sci USA. 107:7401-7406, 2010. PMID: 20385819
HUNT	1023	4x		Krokstad et al. Cohort Profile: the HUNT Study, Norway. Int J Epidemiol. 2013 Aug;42(4):968-77
SiSu + Kuusamo (FINLAND)	1918	4x	http://www.sisuproject.fi/	Vartiainen, E. et al. Thirty-five-year trends in cardiovascular risk factors in Finland. Int. J. Epidemiol. 39, 504-518 (2010). Pajunen, P. et al. The metabolic syndrome as a predictor of incident diabetes and cardiovascular events in the Health 2000 Study. Diabetes Metab. 36, 395-401 (2010).
INGI-FVG	250	4-10x	http://www.netg	Esko,T. et al. Genetic

			ene.it/ita/ingi.asp	characterization of northeastern Italian population isolates in the context of broader European genetic diversity. Eur J Hum Genet. 2013 Jun;21(6):659-65. doi: 10.1038/ejhg.2012.229. Epub 2012 Dec 19
INGI-VB	225	6x	http://www.netgene.it/ita/ingi.asp	Colonna V, et al. Small effective population size and genetic homogeneity in the Val Borbera isolate. Eur J Hum Genet. 2013 Jan;21(1):89-94.
MCTFR	1325	10x	https://mctfr.psych.umn.edu/	Vrieze, S. I. et al. In search of rare variants: preliminary results from whole genome sequencing of 1,325 individuals with psychophysiological endophenotypes. Psychophysiology 51, 1309–1320 (2014).
HELIC	247	4x (1x)	http://www.helic.org/	Panoutsopoulou K, et al. Genetic characterization of Greek population

				isolates reveals strong genetic drift at missense and trait-associated variants. Nat Commun. 2014 Nov 6;5:5345. doi: 10.1038/ncomms6345.
ORCADES	398	4x	http://www.orcades.ed.ac.uk/orcades/	McQuillan, R., et al. (2008). Runs of homozygosity in European populations. American Journal of Human Genetics, 83(3), 359–372. http://doi.org/10.1016/j.ajhg.2008.08.007
InCHIANTI	676	7x	http://www.inchiantistudy.net/bindex.html	Ferrucci L, et al. (2000) Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. J Am Geriatr Soc 48: 1618–1625.
GECCO	1130	4-6x	https://www.fhcrc.org/en/labs/phs/projects/cancer-prevention/projects/gecco.html	Hays J et al. The Women's Health Initiative recruitment methods and results. Ann Epidemiol

				2003;13:S18- S77. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998;19:61-109.
GPC	697	30x		Pato et al. The genomic psychiatry cohort: partners in discovery. Am J Med Genet B Neuropsychiatr Genet. 2013 Jun;162B(4):306-12.
ProjectMinE	935	45x	http://projectmine.com	n/a
NEPTUNE	402	4x	http://www.neptune-study.org/	Design of the Nephrotic Syndrome Study Network (NEPTUNE) to evaluate primary glomerular nephropathy by a multidisciplinary approach. (2013). Kidney Int, 83(4), 749–756.
Totals	**32488**			

Supplementary Table 1 : Table detailing studies that contributed datasets to the HRC. Details of study size, sequencing depth, webpages of studies and primary references are given.

Sites	**Samples**	REF/REF	REF/ALT	ALT/ALT	NRD
1000GP3	**1000GP3 (N=2,525)**	0.10	0.61	0.43	0.70
	HRC Pilot (N=13,309)	0.07	0.36	0.27	0.43
	HRC full (N=32,905)	0.06	0.34	0.25	0.41
HRC MAC5	**1000GP3 (N=2,525)**	0.10	0.59	0.40	0.67
	HRC Pilot (N=13,309)	0.06	0.38	0.26	0.43
	HRC full (N=32,905)	0.06	0.36	0.24	0.41
HRC MAC5 + site filters	**1000GP3 (N=2,525)**	0.10	0.59	0.40	0.67
	HRC Pilot (N=13,309)	0.06	0.36	0.25	0.42
	HRC full (N=32,905)	0.06	0.34	0.23	0.39

Supplementary Table 2: Evaluation of genotype calling process. The table reports percentage discordance of genotypes called using different sites lists (Sites column) and sample sets (Samples column). NRD = non reference allele discordance percentage.

Imputation Panel	0<=MAF<1%	1%<=MAF<5%	5%<=MAF	Total
1000GP3	3,488,324	1,930,001	5,309,997	10,728,322
HRC v1	7,833,143	2,243,365	5,425,008	15,501,516
HRC v1 (only SNPs in 1000GP3)	5,734,139	2,231,559	5,399,097	13,364,795

Supplementary Table 3 : Summary of imputed variants in the InCHIANTI study. The table shows the numbers of SNPs imputed with an imputation $r^2 \geq 0.5$ in the 1,210 samples from the InCHIANTI study using the 1000 Genomes Phase 3 panel (1000GP3) and the HRC panel (HRC v1). The third row of the table shows results for the HRC v1 panel restricted to only those SNPs in the 1000GP3 panel.

				1000G Imputation		HRC imputation (full HRC panel)			HRC imputation (no InCHIANTI samples)			
Trait	**SNP chr:bp (build 37)**	**Nearest Gene**	**InCHIANTI MAF**	**P-value**	**r^2**	**Effect Size (SD)**	**SE**	**P-value**	**Effect Size (SD)**	**SE**	**P-value**	**r^2**
Lactic Dehydrogenase	3:52551566	*STAB1*	0.006	$3x10^{-05}$	0.74	2.37	0.29	$6x10^{-16}$	2.28	0.28	2.83E-15	0.69
Magnesium	17:9689132	*DHRS7C*	0.004	*	0.01	2.26	0.38	$4.5x10^{-09}$	*	*	*	0.47
Resistin	16:17685354	*XYLT1*	0.009	$1.2x10^{-06}$	0.79	1.36	0.24	$1.9x10^{-08}$	1.44	0.27	1.87E-07	0.76
Free Thyroxine (FT4)	9:7092298	*KDM4C*	0.002	*	*	3.26	0.58	$2x10^{-08}$	*	*	*	0.32
Vitamin D	19:11599979	*ZNF653*	0.013	$1.4x10^{-05}$	0.59	1.47	0.19	$2.8x10^{-08}$	1.15	0.21	6.14E-08	0.84
Retinol	11:19870163	*NAV2*	0.004	*	*	1.79	0.32	$3x10^{-08}$	*	*	*	0.00
	5:129871638	*CHSY3*	0.002	*	0.41	2.8	0.5	$3.6x10^{-08}$	2.64	0.48	4.40E-08	0.81
β-Globulins	15:100810864	*ADAMTS17*	0.005	$2x10^{-07}$	0.53	1.71	0.31	$3.6x10^{-08}$	1.53	0.30	3.13E-07	0.72
Potassium	11:102811514	*MMP13*	0.006	$1.2x10^{-06}$	0.77	1.43	0.26	$3.7x10^{-08}$	1.71	0.31	2.65E-08	0.77

Supplementary Table 4 : Potentially novel associations in the InCHIANTI study found by imputing SNPs using HRC release 1. The table lists the trait being tested and summary information about the SNP and the association signal. Imputation was carried out using 2 versions of the HRC panel (with and without the InCHIANTI samples in HRC). Some SNPs were excluded from analysis (denoted by *) due to not being present in panel or having low imputation quality ($r^2 < 0.5$)

	Trait	Lactic Dehydrogenase	Potassium
	SNP chr:bp (build 37)	3:52551566	11:102811514
	Effect/Other Allele	C/G	A/G
	Nearest Gene	*STAB1*	*MMP13*
InCHIANTI Discovery	BETA (SD)	-2.366	-1.434
	SE	0.289	0.259
	P-value	6.17E-16	3.66E-08
	EAF	0.006	0.006
	N	1206	1206
	Imp. Quality	0.79	0.94
SHIP Replication	BETA (SD)	-1.389	-0.549
	SE	0.315	0.200
	P-value	1.14E-05	0.00619879
	EAF	0.003	0.003
	N	1750	4052
	Imp. Quality	0.699	0.781
SHIP TREND Replication	BETA (SD)	-2.762	-0.613
	SE	0.400	0.379
	P-value	9.07E-12	0.106128
	EAF	0.003	0.004
	N	984	984
	Imp. Quality	0.747	0.849
META-ANALYSIS	BETA (SD)	-2.107	-0.841
	SE	0.188	0.146
	P-value	3.78E-29	8.77E-09
	EAF	0.004	0.004
	N	3940	6242

Supplementary Table 5 : Replication results for InCHIANTI GWAS for the 93 circulating blood marker phenotypes. The table shows results for the 2 SNPs that replicated in either the SHIP or SHIP TREND samples. The final meta-analysis results across the 3 cohorts are reported.

Imputation Panel	Effect size (SDs)	p-value	Imputation quality
HRC release 1	**-2.07**	**$2x10^{-13}$**	**0.98**
1000GP3	**-1.86**	**$3x10^{-11}$**	**0.87**
HapMap2	-	-	-

Supplementary Table 6 : Summary of association signal at SNP rs28929474 using imputed data from 3 different reference panels. The SNP does not exist in the HapMap2 panel.

Site List	Source/Type
Human CNV370-Quad	Chip (Illumina)
Human 660W-Quad	Chip (Illumina)
Human OmniExpress	Chip (Illumina)
Human Omni1-Quad	Chip (Illumina)
Human Omni5	Chip (Illumina)
Human CoreExome	Chip (Illumina)
Metabochip	Chip (Illumina)
Affy_Genome-Wide Human SNP Nsp/Sty	Chip (Affy)
Affy Genome-Wide Human SNP Array 6.0	Chip (Affy)
UK Biobank	Biobank Study
GIANT Consortium	GWAS Study
Global Lipids Genetics Consortium	GWAS Study

Supplementary Table 7 : List of commercial genotyping arrays and study lists used to add SNPs back in after site filtering.

Number of samples	Studies		Removal choice
5	AMD	AMD	Removed the duplicates randomly.
36	IBD	IBD	These were duplicates between Crohns and UC studies. Removed the duplicates randomly.
5	FINLAND	FINLAND	Removed lower coverage (4x) Kuusamo samples in preference to the higher coverage (6x) SiSu samples.
14	GECCO	GECCO	Removed the duplicates randomly.
17	GoT2D	FINLAND	Removed the FINLAND samples.
79	GoT2D	UK10K	Removed the UK10K/UK10K duplicates, then removed randomly otherwise.
34	GPC	BRIDGES	Removed the GPC samples.
32	GPC	GPC	Removed the duplicates randomly.
14	MCTFR	MCTFR	Removed the duplicates randomly.
1	NEPTUNE	NEPTUNE	Removed the duplicates randomly.
1	ORCADES	1000GP3	Removed the ORCADES sample.
1	ProjectMinE	GoNL	Removed the ProjectMinE sample.
1	ProjectMinE	ProjectMinE	Removed the duplicates randomly.
3	SardinIA	SardinIA	Removed the duplicates randomly.
26	UK10K	UK10K	These were monozygotic twins already

			identified by UK10K. Removed based on a list from UK10K of samples they had already excluded from downstream analysis.

Supplementary Table 8 : Details of duplicate removal. Each row of the table details the number of duplicate pairs found within and between studies together with the method by which duplicates were removed.

Supplementary Note

The section contains acknowledgements for some of the cohorts

NEPTUNE

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GECCO

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HELIC

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ORCADES

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GoT2D

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IBD

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Project MinE

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AMD

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MCTFR

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SISu and Kuusamo

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INGI-VB

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Genomic Psychiatry Cohort

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