Chapter 5

T1D GWAS

5.1 Methods

Our collaborators (Dr Maria Loredana Marcovecchio and Professor David Dunger, University of Cambridge) provided us with access to genotype data for T1D patients in three genotyping groups: 192 samples in "Group 1", 1194 samples in "Group 2" and 967 samples in "Group 3".

5.1.1 Groups 1 and 2

The data for samples in groups 1 and 2 had already been quality controlled and I included an additional quality control (QC) step to remove 7 SNPs in group 1 and 244 SNPs in group 2 which were flagged by PLINK (version 1.9) (Purcell et al., 2007) as heterozygous in males but did not reside in the pseudo-autosomal region of chromosome X (Table 5.1).

I used the Michigan Imputation Server (Das et al., 2016) to impute missing genotypes for samples in groups 1 and 2, using the Haplotype Reference Consortium (HRC) panel of 64,976 human haplotypes at 39,235,157 SNPs as the reference data (version r1.1 2016) (McCarthy et al., 2016). To prepare the data for imputation I used the `HRC-1000G-check-bim.pl` script written by Will Rayner (https://www.well.ox.ac.uk/~wrayner/tools/), which updates the strands, alleles and genomic coordinates of the variants to reflect HRC/hg19, and removes variants with large differences in allele frequencies compared to HRC ($> 20\%$) or ambiguous alleles (AT/GC variants with MAF$> 40\%$). I then used the `VcfCooker` tool (https://genome.sph.umich.edu/wiki/VcfCooker) to convert the data to per-chromosome bgzip `VCF` files for input into the imputation server, and specified that the samples were of European ancestry and that any variants with low imputation quality ($R^2 < 0.3$) should be discarded. I ran the imputation job on the server in the "QC and imputation mode" with phasing using Eagle version 2.4 (Loh et al., 2016). After completion, I downloaded the imputed data and used

the `ic.pl` script written by Will Rayner (https://www.well.ox.ac.uk/~wrayner/tools/) to check the quality of the results. The post-imputation QC reports are publicly available (group 1: https://github.com/annahutch/T1D-GWAS/blob/main/Group1.html, group 2: https://github.com/annahutch/T1D-GWAS/blob/main/Group2.html) and show that the imputed data is of high quality.

Following imputation I removed samples with extreme proportions of homozygous variants, defined as < 0.828 or > 0.834 in group 1 (Fig. 5.1A) and > 0.888 in group 2 (Fig. 5.2A), since low proportions may indicate low sample quality whilst high values may indicate inbreeding. I also removed 321,570 monomorphic SNPs in group 1 (Fig. 5.1B) and 532,889 monomorphic SNPs in group 2 (Fig. 5.2B), but kept a list of these SNPs so that they could be added back into the analysis later on, depending on the analysis strategy.

Deviations from Hardy-Weinberg equilibrium (HWE) are likely to be the consequence of genotyping error, inbreeding or population stratification (Wigginton et al., 2005). Since the samples in groups 1 and 2 with evidence of inbreeding (quantified by high homozygosity proportions) had already been removed, and those of non-European ancestry had also been removed (Table 5.1), it was likely that any deviations from HWE at this stage of the analysis were due to genotyping errors. Generally, departure from HWE is examined in control samples (i.e. those without the disease in a case-control GWAS setting) because SNPs that strongly associate with the trait of interest are not expected to be in HWE in case samples. However, all samples in groups 1 and 2 were T1D cases, and so no control data was available. In group 1, the minimum HWE p-value was $1.412e-07$ (Fig. 5.1C), whilst for group 2 the minimum HWE p-value was $3.935e-17$ (Fig. 5.2C). All of the 287 SNPs in group 2 with HWE $p < 1e-10$ resided on either chromosome 6 or the X chromosome (Fig. 5.2D). This was reassuring because it is known that the MHC strongly associates with T1D and so the SNPs with evidence of departure from HWE on chromosome 6 are likely reflecting the strong association of the MHC with T1D. Moreover, PLINK only uses female samples to evaluate departure from HWE for SNPs residing on the X chromosome (since male samples are hemizygous), which may be problematic due to a decrease in power (when the sample sizes of groups 1 and 2 were already small) and for additional reasons as discussed in Graffelman and Weir (2016). I therefore did not filter SNPs by HWE p-value at this stage of the analysis.

The imputed and quality controlled data consisted of 11,483,371 SNPs in 187 samples (group 1) and 16,730,386 SNPs in 1191 samples (group 2). I used the sample ID keys provided by our collaborators to identify the original cohort from which each sample originated. In group 1, 186 samples were from the ORPS cohort and one sample was from the GRID cohort. In group 2, 378 samples were from the AdDIT cohort, 789 were from the NFS cohort and 23 were from the ORPS cohort. There was no sample overlap between groups 1 and 2.

	Group 1		**Group 2**	
	Samples	**SNPs**	**Samples**	**SNPs**
Initial raw genotype files	**200**	**542,585**	**1363**	**547,644**
8.1 Remove SNPs flagged for removal from combined QC		-12,192		-13,975
8.2 Remove subjects flagged for removal from combined QC	-3		-8	
8.3 Remove SNPs that couldn't be mapped to hg19		-12,732		-12,537
8.4 Flip SNPs to align from hg19+ to 1KG+		189,935 flipped		191,688 flipped
8.7 Update SNP names from hg19 to 1KG		383,483 updated		386,881 updated
8.9 Remove SNPs flagged for removal from study-specific QC		-222,025		-162,261
8.10 Remove subjects fagged for removal from study-specific QC	-2		-32	
8.11 Update sex of subjects if needed	0 updated		0 updated	
8.12 Exclude samples of non-European ancestry	-3		-129	
Remove problematic SNPs flagged as heterozygous haploid		-17		-244
Final data	**192**	**296,233**	**1194**	**359,529**

Table 5.1 Table describing the QC steps implemented for genotype data for samples in groups 1 and 2, including the number of SNPs or subjects that were affected in each step. Step 8.1 removes SNPs with call rates less than 99%, those residing on the Y chromosome in female samples, those with Mendel inconsistencies, those with concordant rates less than 99%, those with Y call rates less than 99% and those in Hardy-Weinberg disequilibrium. Step 8.2 removes subjects mislabeled as male or female and those missing more than 5% of genotypes. Step 8.3 removes SNPs with duplicate positions, allele mismatches, ambiguous alleles, alleles with big frequency differences between cohorts and those with name mismatches. Step 8.9 removes monomorphic SNPs and those in Hardy-Weinberg disequilibrium. Step 8.10 removes samples with extreme heterozygosity values. Steps 8.1 to 8.12 had already been implemented by our collaborators using the `RAW2FiNAL.sh` bash script (written by Rany Salem). I included an additional SNP QC step to remove any problematic heterozygote SNPs.

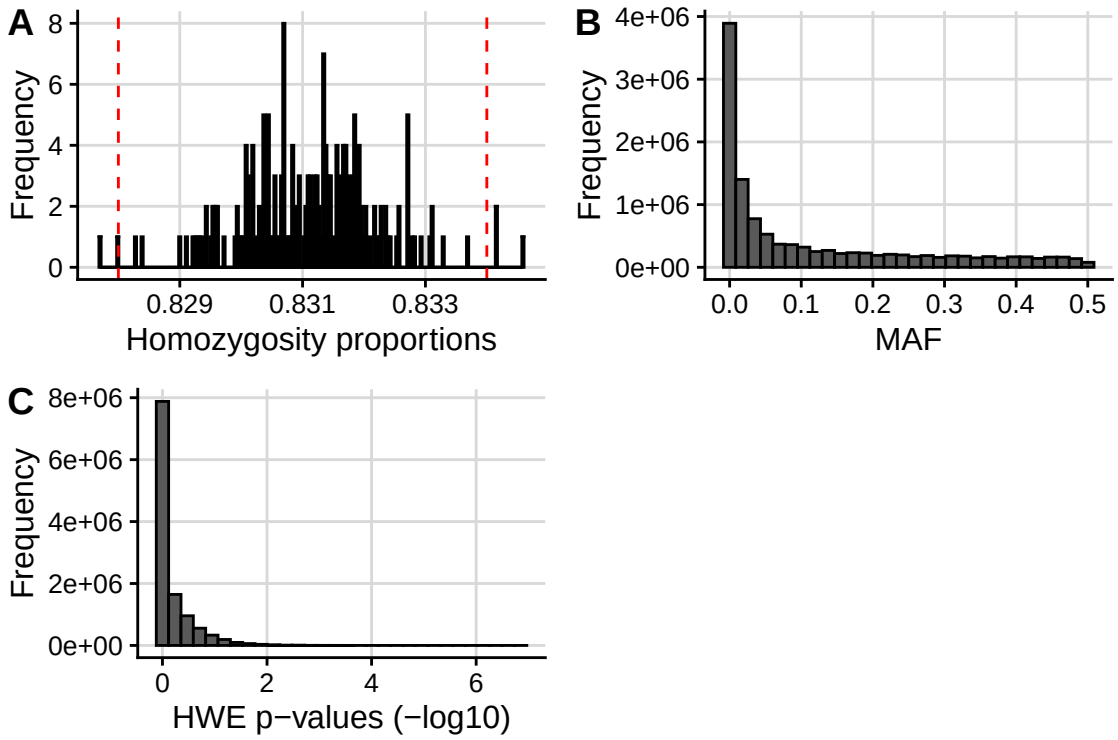

Fig. 5.1 Plots to facilitate post-imputation quality control for samples in genotyping group 1. (A) is a histogram of per-sample homozygosity proportions with red dashed lines showing the thresholds used to remove samples due to extreme homozygosity proportions (< 0.828 or > 0.834). (B) is a histogram of MAF values and (C) is a histogram of HWE p-values.

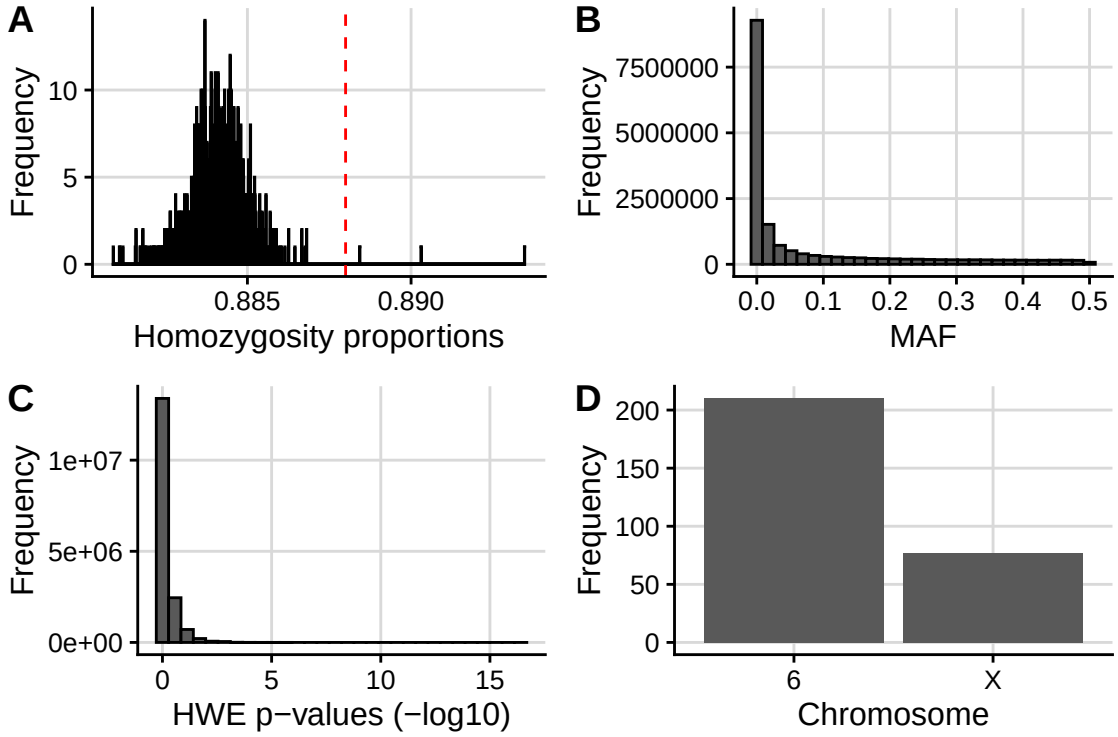

Fig. 5.2 Plots to facilitate post-imputation quality control for samples in genotyping group 2. (A) is a histogram of per-sample homozygosity proportions with a red dashed line showing the threshold used to remove samples due to extreme homozygosity proportions (> 0.888). (B) is a histogram of MAF values and (C) is a histogram of HWE p-values. (D) shows the number of SNPs with HWE $p < 1e-10$ that resided on each chromosome (SNPs with HWE $p < 1e-10$ were only found on chromosomes 6 or X).

5.1.2 Group 3

I downloaded PLINK formatted genotype data for 967 samples in genotyping group 3 and removed any samples with incorrectly formatted sample IDs (13 with "rep**" and 7 with "unq**"). For the 69 remaining samples with replicates within this genotyping group (due to being sequenced on different wells or plates) I selected the replicate with the best SNP coverage. I then converted the data from GRCh38 to hg19 co-ordinates and discarded 2059 SNPs which could not be converted between the builds. The data had not yet been quality controlled and so I implemented a pre-imputation QC pipeline to ensure that the study data used for imputation was of high quality.

Firstly, I removed two samples incorrectly listed as females (Fig 5.3A) and used the inferred sex for 556 samples with missing sex information. I then removed any samples with either $> 3\%$ of SNPs missing or with extreme proportions of homozygous variants (> 0.83) (Fig 5.3B). I checked for any related individuals in the genotyping group by first pruning the variants so that no pair of SNPs within 50-kb were correlated ($r^2 > 0.2$) (using a step size of 5) and then using

the `-genome` flag in PLINK to derive pairwise IBD proportions (Fig 5.3C). I made a list of the related samples but did not remove these at this stage of the analysis, since related samples do not affect imputation results. I also removed SNPs missing in more than 2% of individuals (Fig 5.3D).

I examined the SNPs with small HWE p-values and found that most SNPs with HWE $p < 1e-10$ were on chromosome 6 or chromosome 1 (Fig 5.3E). This is likely due to the fact that all of the samples were T1D cases and that there is a strong association between the MHC (chromosome 6) and *PTPN22* (chromosome 1) with T1D (although it was interesting that chromosome 11 didn't contain more variants with evidence of departure from HWE, due to the strong association of *INS* and T1D). I removed 209 SNPs with HWE $p < 1e-10$ which did not reside on chromosome 6 or in the *PTPN22* gene region (chr6:114,256,433-114,514,381, which covers the *PTPN22* gene plus 100-kb either side) (Fig 5.3F). I also removed 68,397 monomorphic SNPs (Fig 5.3G).

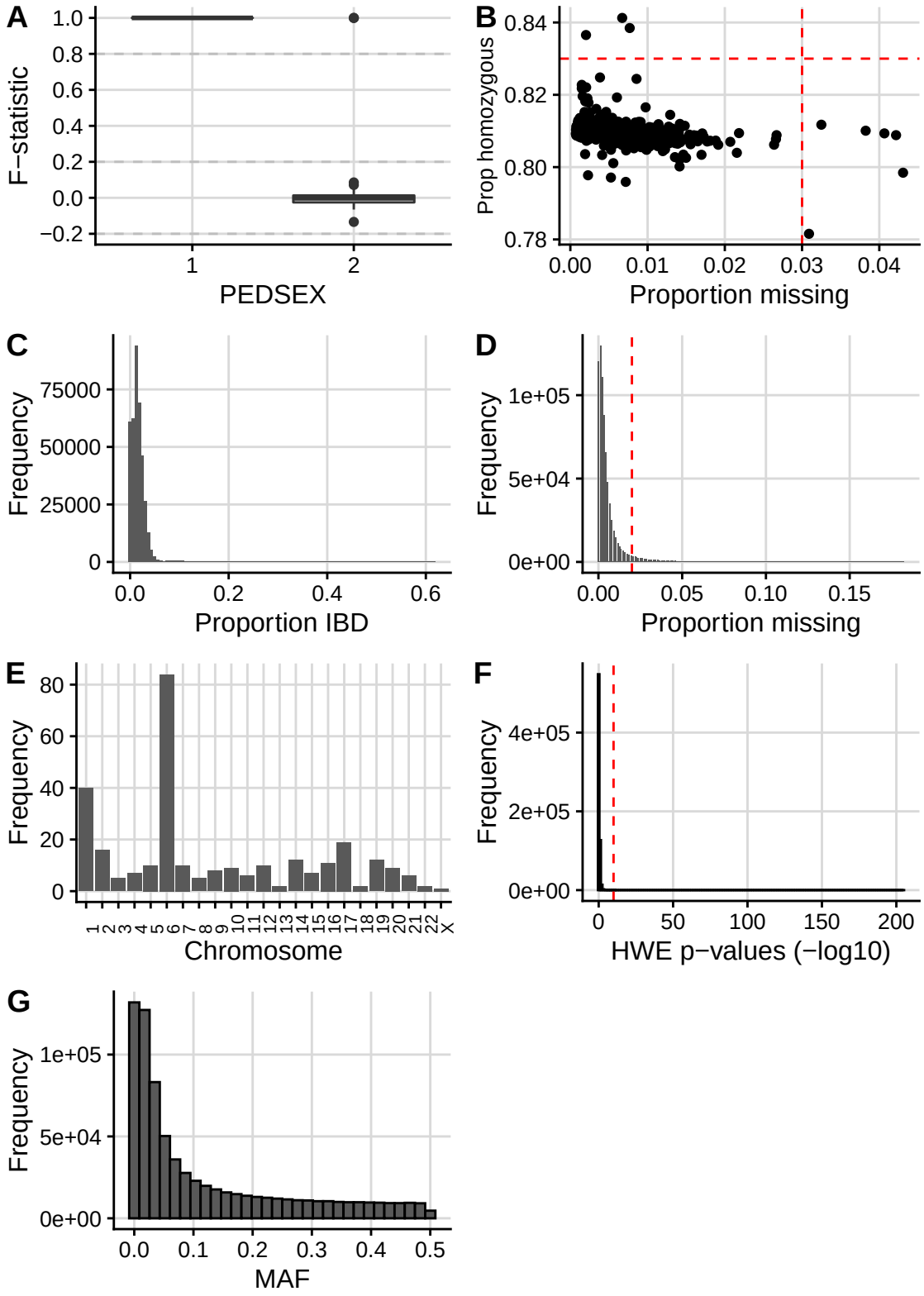

Fig. 5.3 Plots to facilitate pre-imputation QC for samples in genotyping group 3. (A) is a box plot showing the F-statistic (actual X chromosome homozygosity estimate) values for samples labelled as male (PEDSEX=1) and female (PEDSEX=2). A male call is made if $F > 0.8$ and a female call is made if $F < 0.2$ (grey dashed lines). (B) shows per-sample homozygosity proportions against the proportions of SNPs missing in each sample, with red dashed lines showing the thresholds used to remove samples (proportion homozygosity > 0.83 or proportion missing > 0.03). (C) is a histogram of proportion IBD values ($P(IBD = 2) + 0.5 \times P(IBD = 1)$) for each pair of samples use to determine related pairs of individuals. (D) is a histogram of per-SNP missingness with a red dashed line at proportion missing $= 0.02$. (E) shows the number of SNPs with HWE $p < 1e - 10$ on each chromosome. (F) is a histogram of HWE p-values for SNPs not residing on chromosome 6 or in the *PTPN22* gene region (chr6:114256433-114514381) with a red dashed line at HWE $p = 1e - 10$. (G) is a histogram of MAF values.

I next checked for any non-European samples using the 1000 Genomes data as reference. Following the "Ancestry estimation based on reference samples of known ethnicities" vignette (available from https://cran.r-project.org/web/packages/plinkQC/vignettes/AncestryCheck.pdf) from the `plinkQC` R package, I firstly pruned my study data to exclude known regions of high LD and so that no pair of SNPs with 50-kb were correlated ($r^2 > 0.2$) (using a step size of 5). I then filtered the reference data to only contain the pruned SNPs in the study data set and then matched SNPs between the reference data and the study data based on genomic position and alleles. I merged the two data sets and performed PCA using the `-pca` flag in PLINK. I then used the `plinkQC::evaluate_check_ancestry` function to estimate the ancestry of the study samples from the PCA results. Briefly, the function uses principal components 1 and 2 to find the centre of the known European reference samples, and any study samples whose Euclidean distance from the centre falls outside the radius specified by the maximum Euclidean distance of the reference samples multiplied by the chosen `europeanTh` value (default = 1.5) are labelled as non-European. This analysis identified 35 samples as non-European and I excluded these from the analysis (Fig 5.4). The final quality controlled data was for 640,431 SNPs in 834 samples.

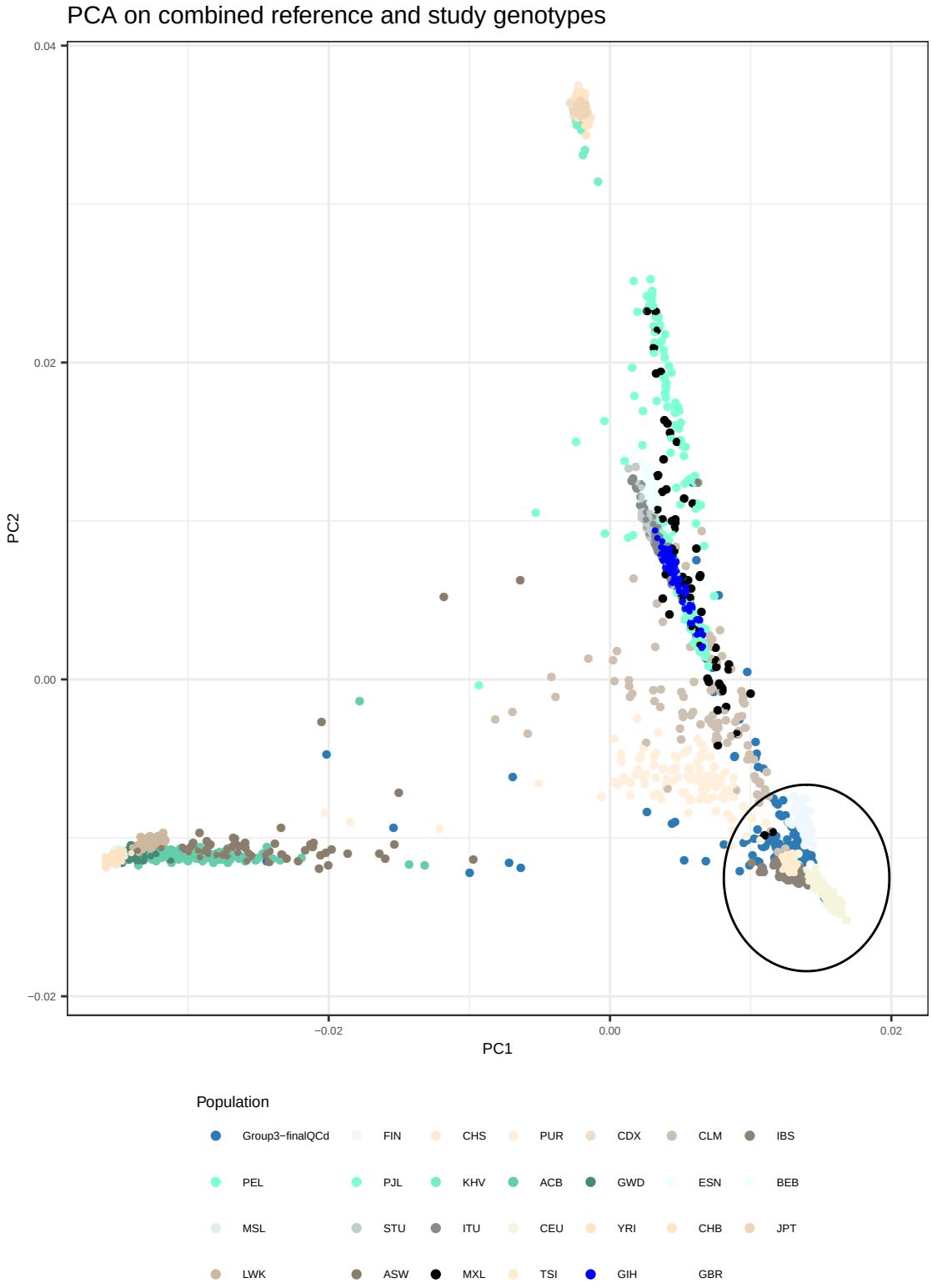

Fig. 5.4 Figure generated using the `plinkQC::evaluate_check_ancestry` function to identify any samples of non-European ancestry, using the 1000 Genomes data as reference.

As before, I used Will Rayner's `HRC-1000G-check-bim.pl` script to prepare the data for imputation, and then used the Michigan Imputation Server (Das et al., 2016) with the HRC reference panel for imputation. The post-imputation QC report generated using Will Rayner's `ic.pl` script is publicly available (group 3: https://github.com/annahutch/T1D-GWAS/blob/main/Group3.html) and shows that the imputed data is of high quality.

Following imputation I removed samples with extreme proportions of homozygous variants, defined as < 0.877 or > 0.885 (Fig. 5.5A) and removed 657,771 monomorphic SNPs (Fig. 5.5B), but kept a list of these SNPs so that they could be added back into the analysis later on, depending on the analysis strategy. For the 302 SNPs with HWE $p < 1e-10$, the vast majority resided on chromosome 6 and the X chromosome as expected, but six resided on chromosome 10 and eight resided on chromosome 18 (Fig. 5.5C, Fig. 5.5D). Upon further investigation, the minimum HWE p-values for SNPs residing on chromosome 10 was $3.491e-12$ and the minimum HWE p-values for SNPs residing on chromosome 18 was $3.372e-26$. Since these p-values were calculated for case samples rather than controls, I chose not to filter SNPs by HWE p-value at this stage. Note that at the *pre*-imputation QC stage of the analysis, SNPs in all three genotyping groups were filtered by HWE p-value to ensure that the study genotypes used in the imputation procedure were of high quality. To ensure that any SNPs prioritised in my analysis are reliably capturing true associations, I will examine the HWE p-value for all prioritised SNPs and implement a retrospective filtering step on HWE p-value if required.

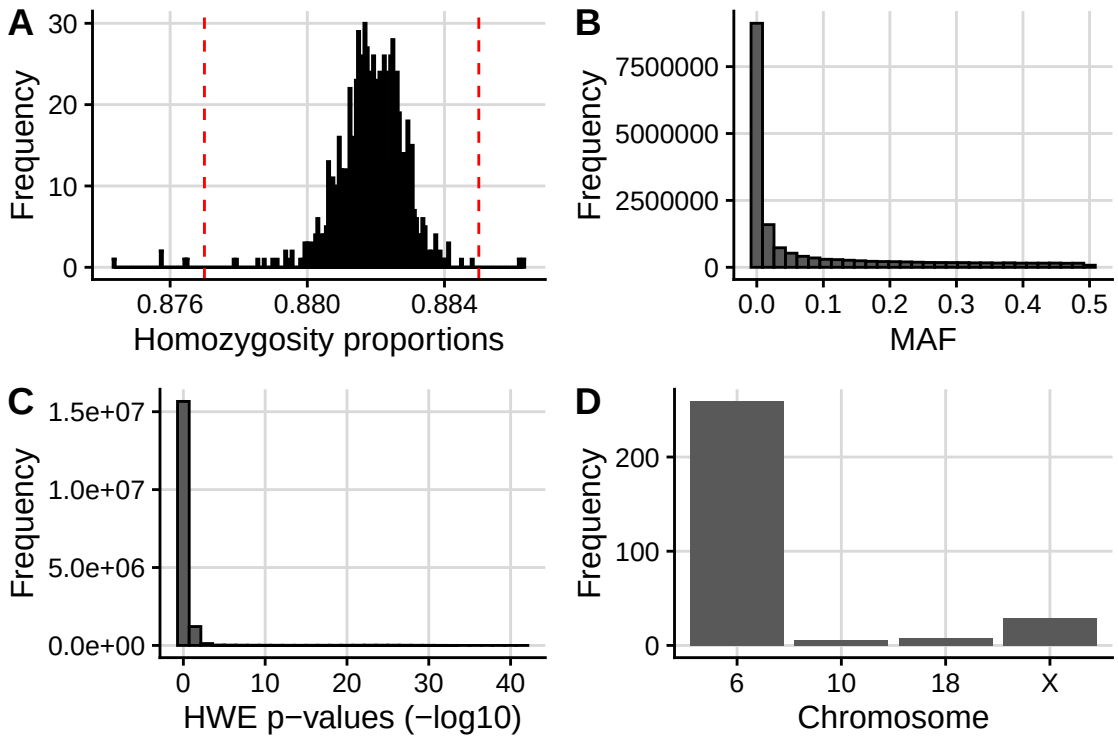

Fig. 5.5 Plots to facilitate post-imputation quality control for samples in genotyping group 2. (A) is a histogram of per-sample homozygosity proportions with a red dashed line showing the threshold used to remove samples due to extreme homozygosity proportions (< 0.877 or > 0.885). (B) is a histogram of MAF values and (C) is a histogram of HWE p-values. (D) shows the number of SNPs with HWE $p < 1e-10$ that resided on each chromosome (SNPs with HWE $p < 1e-10$ were only found on chromosomes 6, 10, 18 or X).

The imputed and quality controlled data for group 3 consisted of 16,583,186 SNPs in 827 samples. I used the sample ID keys provided by our collaborators to identify the original cohort from which each sample originated and found that 166 samples were from the AdDIT cohort, 404 were from the NFS cohort and 256 were from the ORPS cohort. Next I checked whether any of the samples in group 3 were present in groups 1 or 2 (since it is important that each sample appears in exactly one group) and found that 146 of the samples in group 3 were also present in group 1 and an additional 9 samples in group 3 were also present in group 2 (there was no overlap between samples in groups 1 and 2). For samples which were present in more than one genotyping group, I selected the group where the sample has the highest SNP coverage. Thus, the final data is for one GRID sample, 1193 NFS samples, 310 ORPS samples and 544 AdDIT samples (Table 5.2).

Cohort	GRID	NFS	ORPS	AdDIT
Number of samples	1	1193	310	544

Table 5.2 Table listing the number of samples present in each cohort for my T1D GWAS analysis.

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