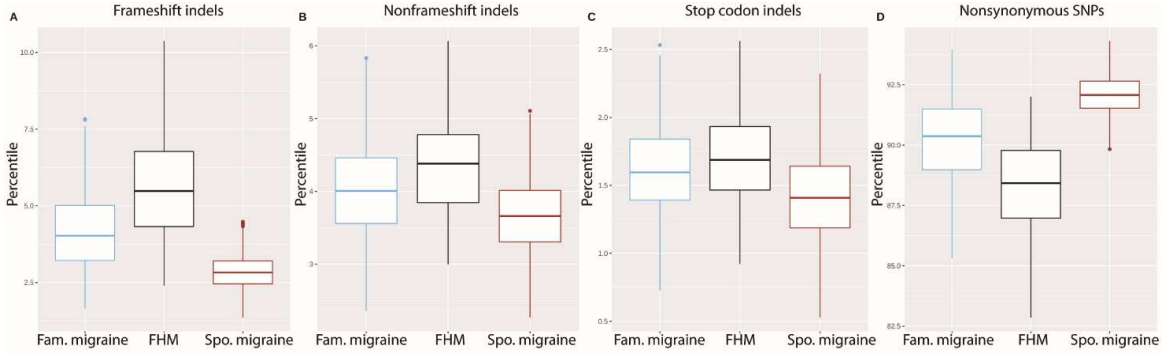
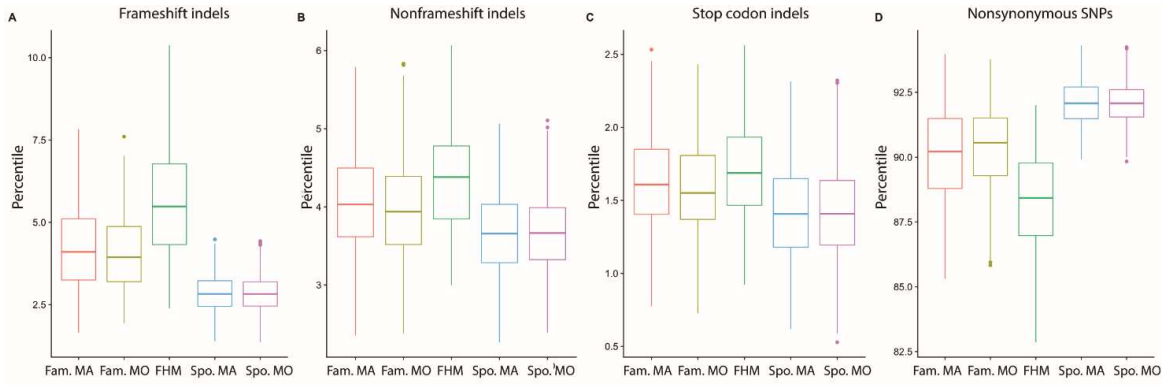
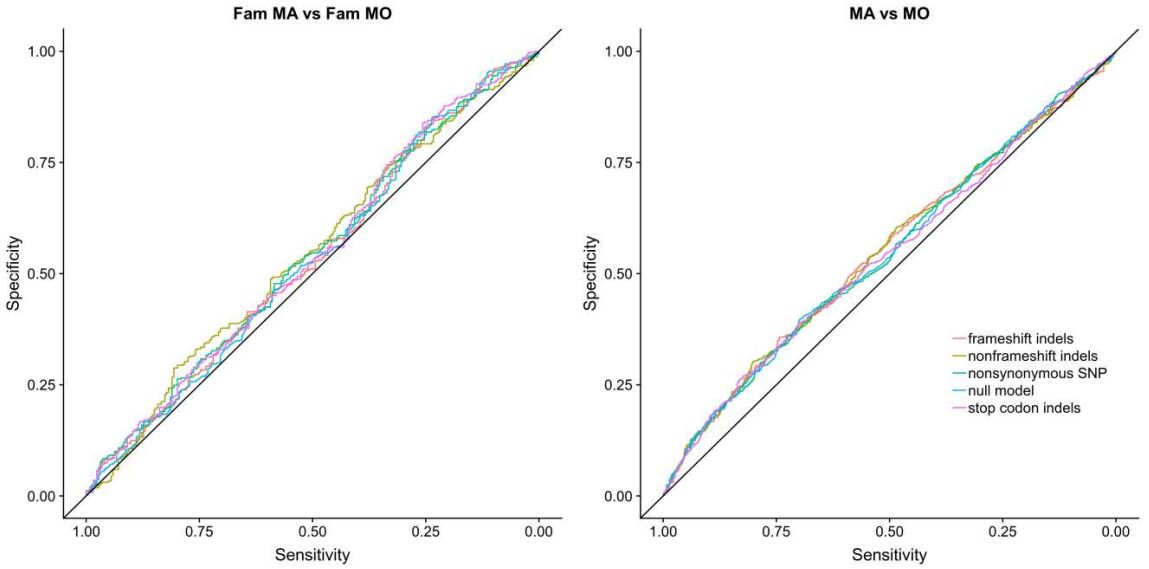
Supplementary



Supplementary figure 1. A-D) Percentile distribution of rare variants within frameshift indels, nonframeshift indels, stop codon indels and nonsynonymous SNPs in FHM, Fam MA&MO and MA&MO. The distribution for each variant subtype is calculated as the percentage of all rare functional variants per individual.



Supplementary figure 2. Boxplots showing the percentage distribution of **A**) rare frameshift indels, **B**) rare nonframeshift indels, **C**) rare stop codon indels and **D**) rare nonsynonymous SNPs in familial MA, familial MO, FHM, sporadic MA (MA) and sporadic MO (MO). The distribution for each variant subtype is calculated as the percentage of all rare functional variants per individual.



Supplementary figure 3. MCMCgrm linear regression. We see no difference of rare variants within frameshift indels, nonframeshift indels, stop codon indels and nonsynonymous SNPs between familial MA and familial MO as well as no difference between sporadic MA and sporadic MO.

Supplementary Table 1. Supplementary_table_1_sex_distribution_age_at_onset_headache.xlsx

Supplementary Table 2. Supplementary_table_2_comparison_of_aura_symptoms.xlsx

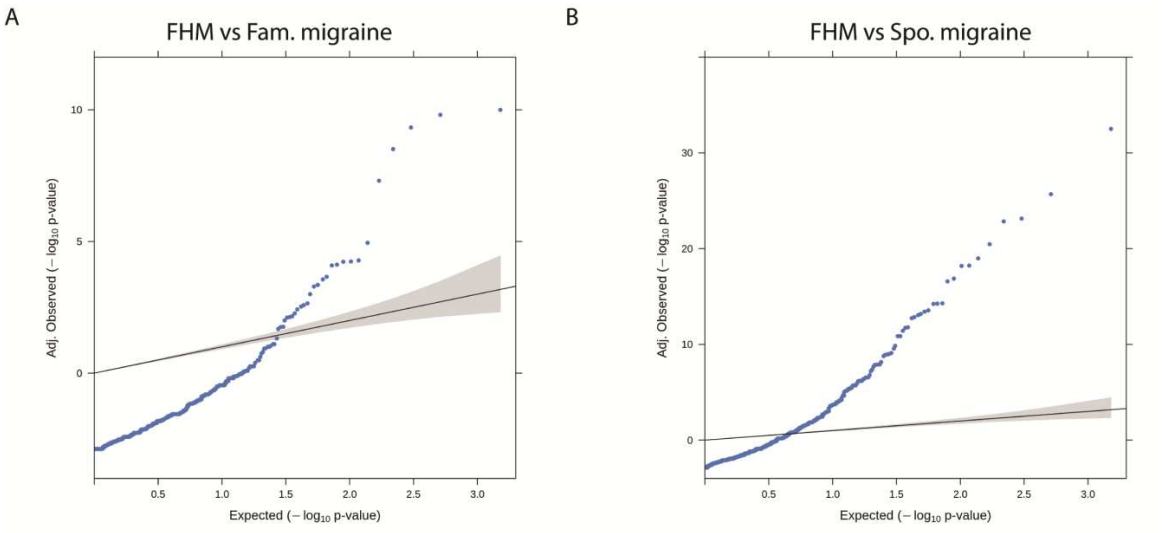
Supplementary Table 3. Results from AUC analysis of MCMCgrm between familial MA and familial MO as well as between sporadic MA and sporadic MO. The difference in percentage is listed for each individual rare variant group analysis together with corresponding adjusted p-value.

Analysis	Rare variant group	Difference (%)	p adj.
Fam. MA vs. Fam. MO	Frameshift indels	-0.0024	1
	Nonframeshift indels	-0.014	0.53
	Stopcodon indels	-0.0095	1
	Nonsynonymous SNP	-0.0094	0.88
Spo. MA vs. Spo. MO	Frameshift indels	-0.0041	1
	Nonframeshift indels	-0.0043	1
	Stopcodon indels	0.0034	1
	Nonsynonymous SNP	0.000603	1

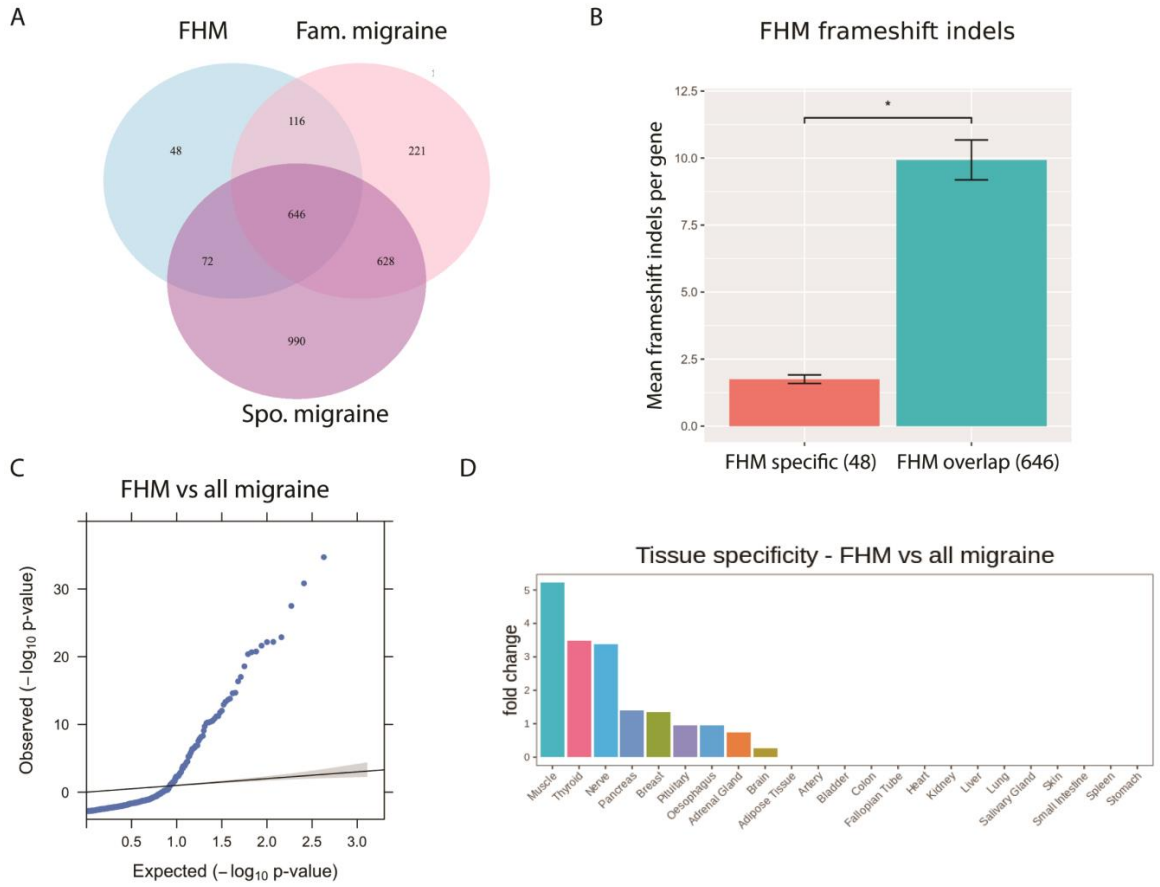
Supplementary table 4. Excel table of overlapping genes between FHM and familial migraine, between FHM and sporadic migraine and between FHM and all migraine, which have more frameshift indels in FHM. Genes_fhm_vs_mamo_fammamo.xlsx

Supplementary Table 5. Table of mean rare functional variant per patient for each patient group as well as the mean MAF for the rare functional variants according to gnomAD v.2. We have also listed the mean of total number of variants per individual for each patient group, which we have used as a covariate in our regression analysis.

Patient group	mean rare functional variant	mean MAF (gnomAD v.2)	mean variant
FHM	1265	0.0168	5026913
Fam. Migraine	1238	0.0172	5021473
Spo. Migraine	1200	0.0176	4999946



Supplementary figure 4. A–B) QQplots of adjusted p-values against expected p-values showing which overlapping genes that have more frameshift indels between FHM and familial migraine and between FHM and sporadic migraine, respectively.



Supplementary figure 5. A) Venn plot showing the number of genes with frameshift indels in FHM, familial migraine, sporadic migraine and the number of overlapping genes. **B)** Bar plot with mean frameshift indels per gene in FHM patients in the 48 FHM-specific genes and in the 646 FHM - all migraine overlapping genes. Asterisk display the significance level (*padj* < *0.05*). **C)** QQplot of adjusted p-values against expected p-values showing number of overlapping genes that have more frameshift indels between FHM and all migraine (sporadic migraine and familial migraine). **D)** Bar plot of gene fold change enrichment of the 73 genes, which had significantly more frameshift indels in FHM compared to all migraine (sporadic migraine and familial migraine) in 23 human tissues from the GTEx RNA-seq database.