## Supplementary material

**Table 1** Overview of investigated genes and genetic variants considered for the complete study population and the specific cardiovascular drug collectives. Genes marked in grey were only considered in quality control evaluations.

| Collective | Gene | Marker | Collective | Gene | Marker |
|---|---|---|---|---|---|
| **Complete study population & Anticoagulant/antiplatelet collective** | *CYP2C19* | rs4244285 | **Complete study population** | *CYP2D6* | rs72549353 |
| | *CYP2C19* | rs28399504 | | *CYP2D6* | rs5030865 |
| | *CYP2C19* | rs56337013 | | *CYP2D6* | rs5030656 |
| | *CYP2C19* | rs4986893 | | *CYP2D6* | rs28371706 |
| | *CYP2C19* | rs72552267 | | *CYP2D6* | rs72549354 |
| | *CYP2C19* | rs41291556 | | *CYP2D6* | rs1135840 |
| | *CYP2C19* | rs72558186 | | *CYP2D6* | rs5030862 |
| | *CYP2C19* | rs12248560 | | *CYP2D6* | rs16947 |
| | *CYP2C9* | rs7900194 | | *CYP2D6* | rs5030867 |
| | *CYP2C9* | rs72558187 | | *CYP2D6* | rs1065852 |
| | *CYP2C9* | rs1057910 | | *CYP2D6* | rs35742686 |
| | *CYP2C9* | rs9332239 | | *CYP2D6* | rs28371725 |
| | *CYP2C9* | rs9332131 | | *CYP2D6* | rs5030655 |
| | *CYP2C9* | rs72558190 | | *CYP2D6* | rs3892097 |
| | *CYP2C9* | rs28371685 | | *CYP2D6* | rs59421388 |
| | *CYP2C9* | rs56165452 | | *CYP2D6* | rs28371735 |
| | *CYP2C9* | rs28371686 | | *CYP2D6* | rs5030863 |
| | *CYP2C9* | rs72558188 | | *CYP2D6* | rs72549357 |
| | *CYP2C9* | rs1799853 | | *CYP2D6* | dup4125_4133 |
| | *VKORC1* | rs9923231 | | *CYP1A2* | rs762551 |
| **Complete study population & Anticoagulant/antiplatelet collective & Cholesterol lowering drug collective** | *ABCB1* | rs1045642 | | *CYP1A2* | rs56107638 |
| **Complete study population & Cholesterol lowering drug** | *SLCO1B1* | rs4149056 | | *CYP1A2* | rs12720461 |
| | *CYP3A4* | rs55785340 | | *CYP1A2* | rs2069514 |
| | *CYP3A4* | rs35599367 | | *CYP1A2* | rs72547513 |
| | *CYP3A4* | rs4987161 | | *CYP2B6* | rs28399499 |
| | *CYP3A5* | rs776746 | | *CYP2B6* | rs3745274 |
| | *CYP3A5* | rs28365083 | | | |
| | *CYP3A5* | rs41303343 | | | |
| | *CYP3A5* | rs10264272 | | | |

Quality control plots of PGx Data (Agena Bioscience)

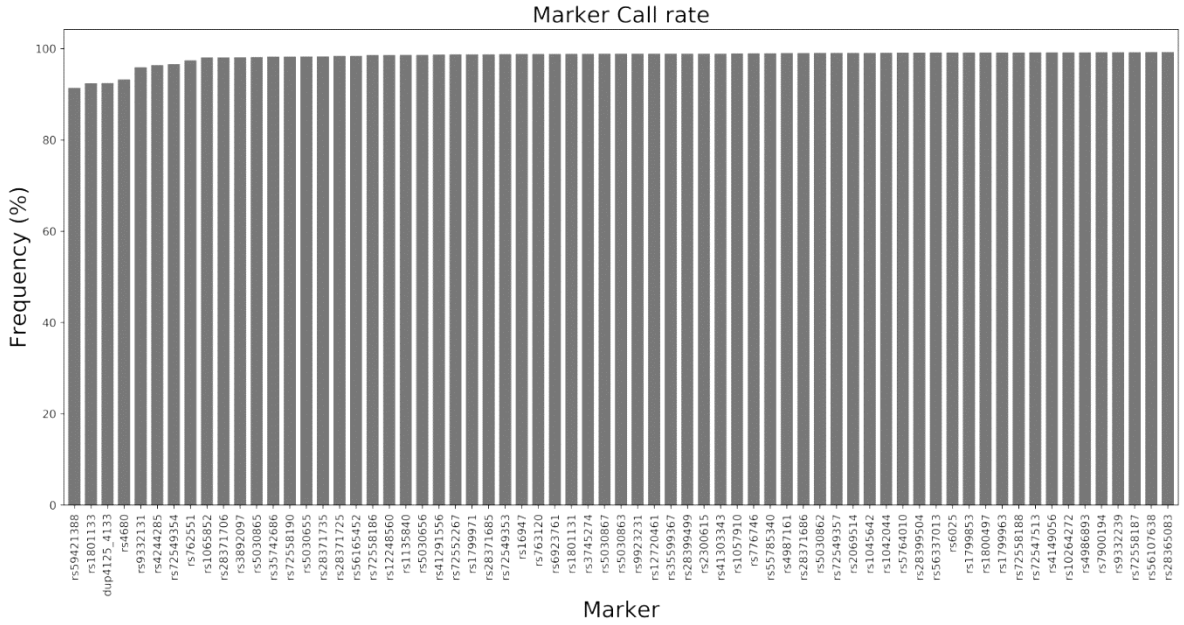


**Figure 1** Marker call rates of all investigated markers (Agena Bioscience)

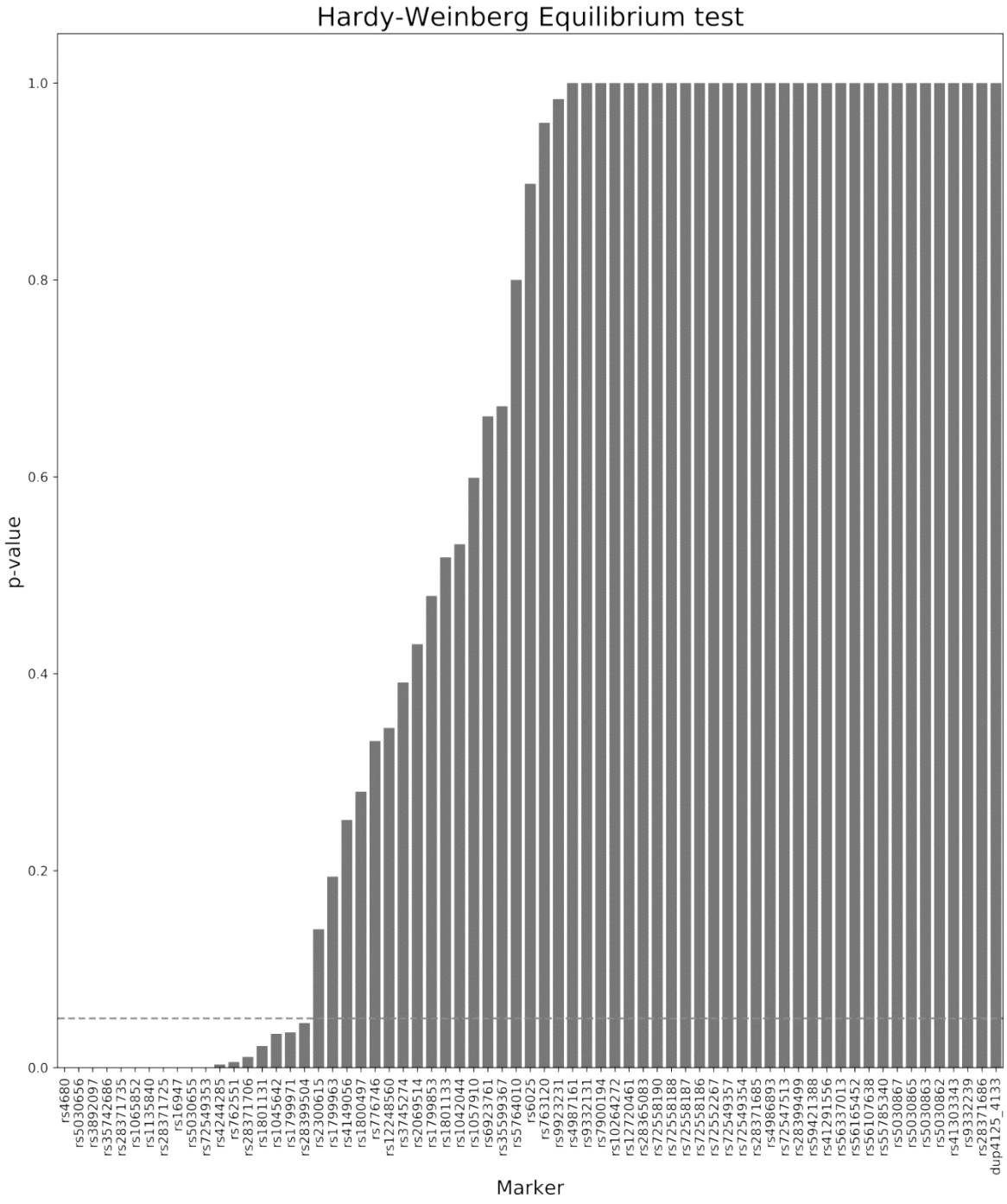


**Figure 2** Hardy Weinberg Equilibrium test results of all investigated markers. For *CYP2D6* 10 of 17 markers were observed to be not in equilibrium. Several variants of that fraction represent reduced function or non-functional alleles. Especially the markers rs5030656 (*9) and rs5030655 (*6) represent specific variants and were observed with low frequencies among Europeans (Whirl-Carrillo et al, 2012). Furthermore, two markers were observed for *CYP2C19* which are not in equilibrium as well. Among them, rs4244285 (*2) encoding for poor functional- and rs28399504 (*4) encoding for non-function activity. In addition, rs762551 (*CYP1A2*) was not accounted to be in HWE.

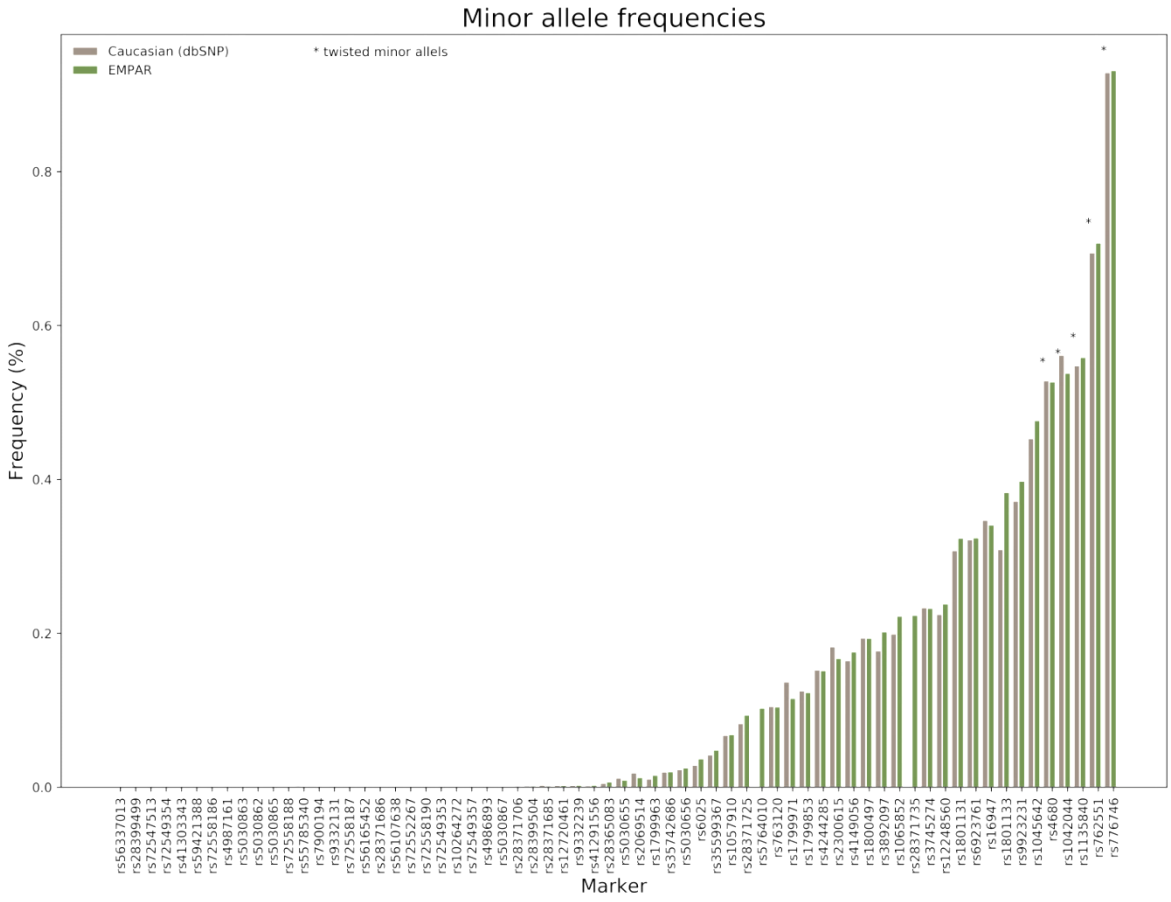


**Figure 3** Minor allele frequencies of all investigated markers compared to Caucasian dbSNP frequencies

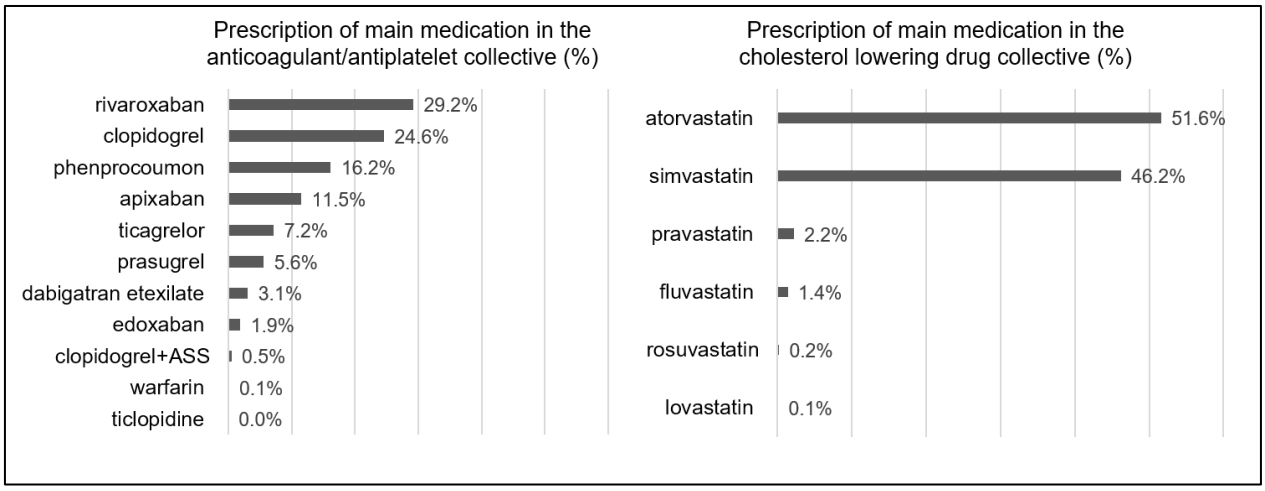


**Figure 4** Percentage of the most frequent prescriptions of main medication in the anticoagulant/antiplatelet and the cholesterol lowering drug collective. ASS: acetylsalicylic acid.

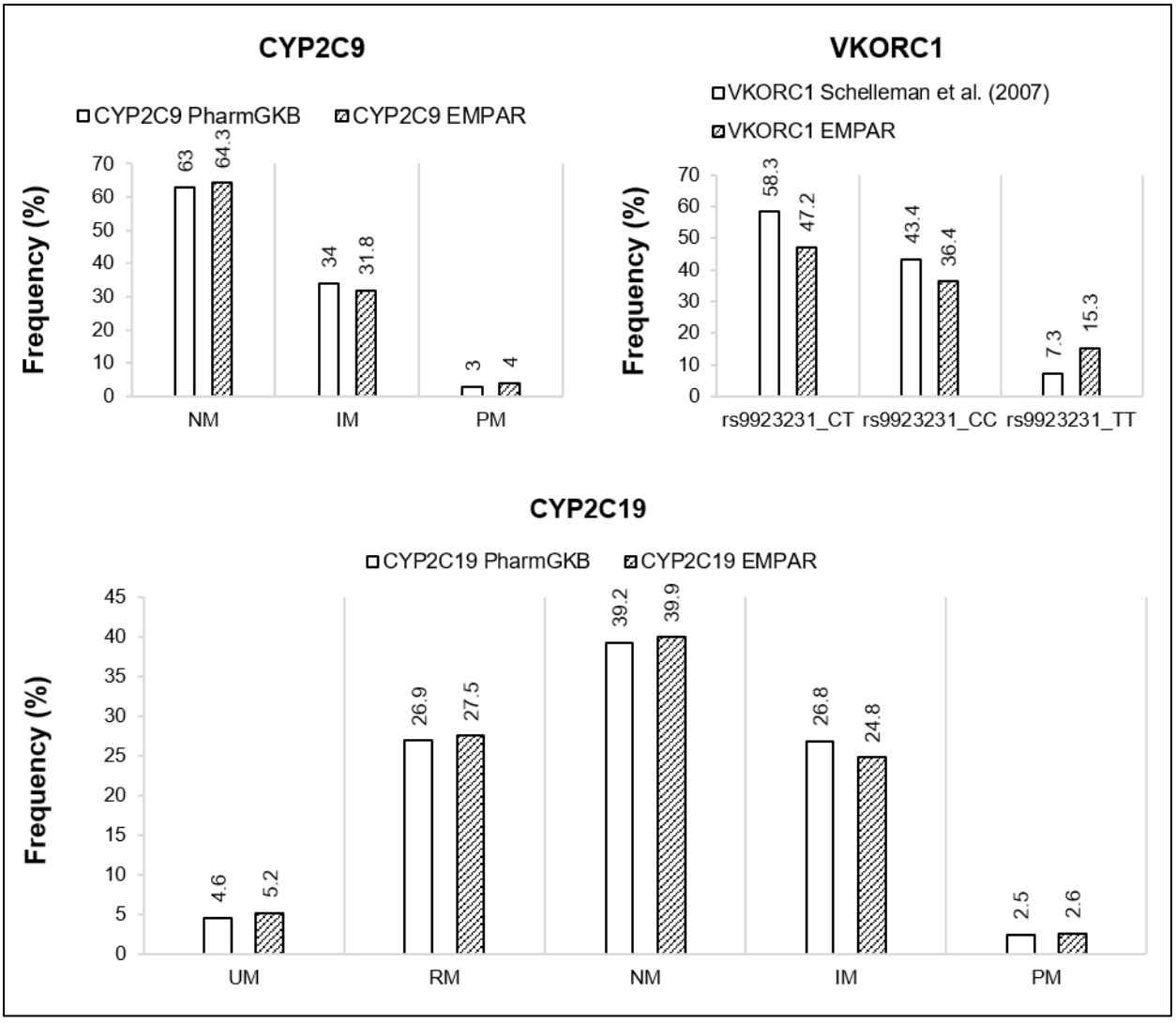


**Figure 5** Frequencies of computed metabolic profiles of genes involved in anticoagulant/antiplatelet metabolism (*CYP2C19, CYP2C9* and *VKORC1*) compared to reference data. UM: ultra-rapid metabolizer, RM: rapid metabolizer, NM: normal metabolizer, IM: intermediate metabolizer, PM: poor metabolizer

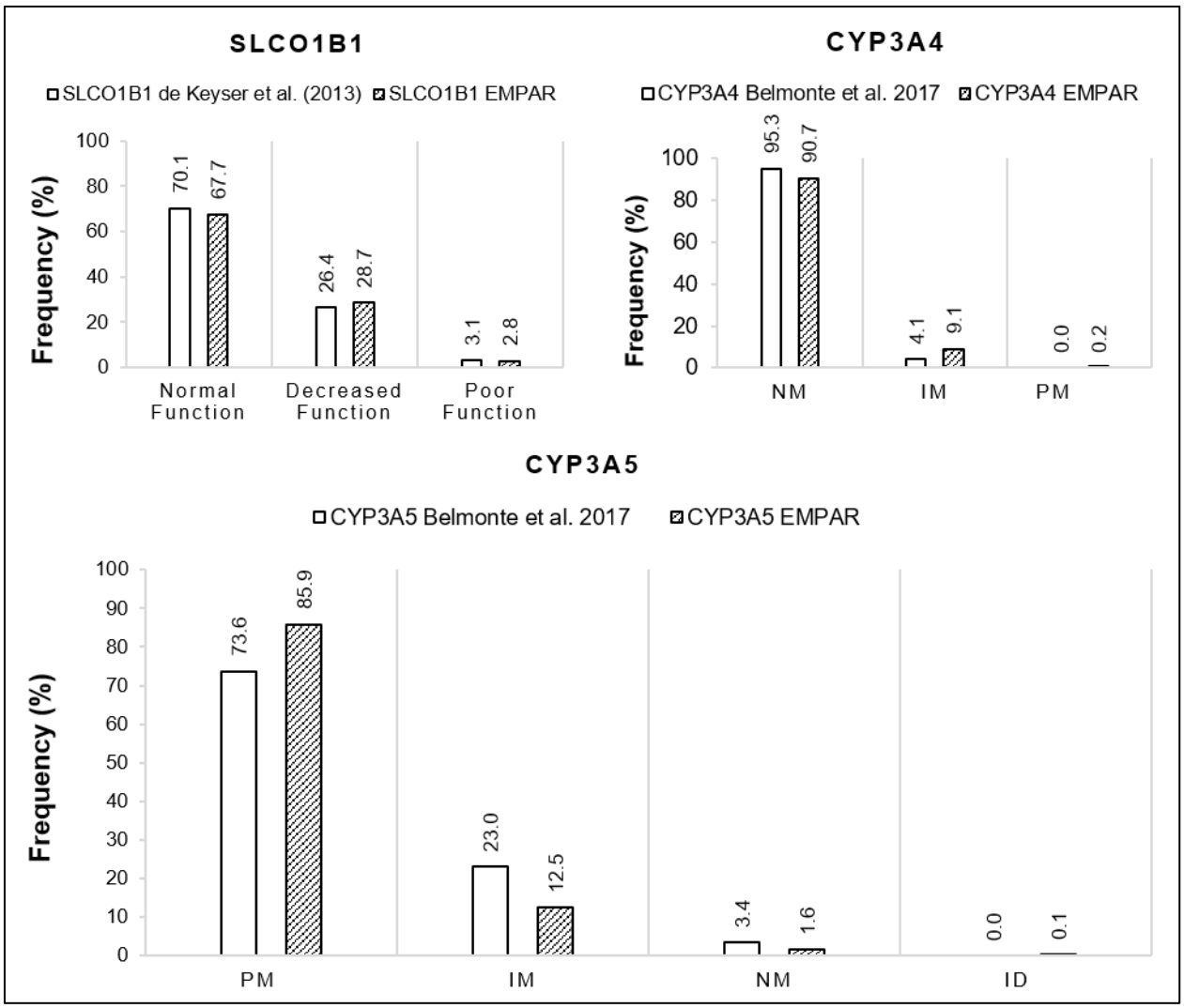


**Figure 6** Frequencies of computed metabolic profiles involved in statin metabolism or transport (*CYP3A4, CYP3A5* and *SLCO1B1*) compared to reference data. NM: normal metabolizer, IM: intermediate metabolizer, PM: poor metabolizer, ID: intermediate metabolizer

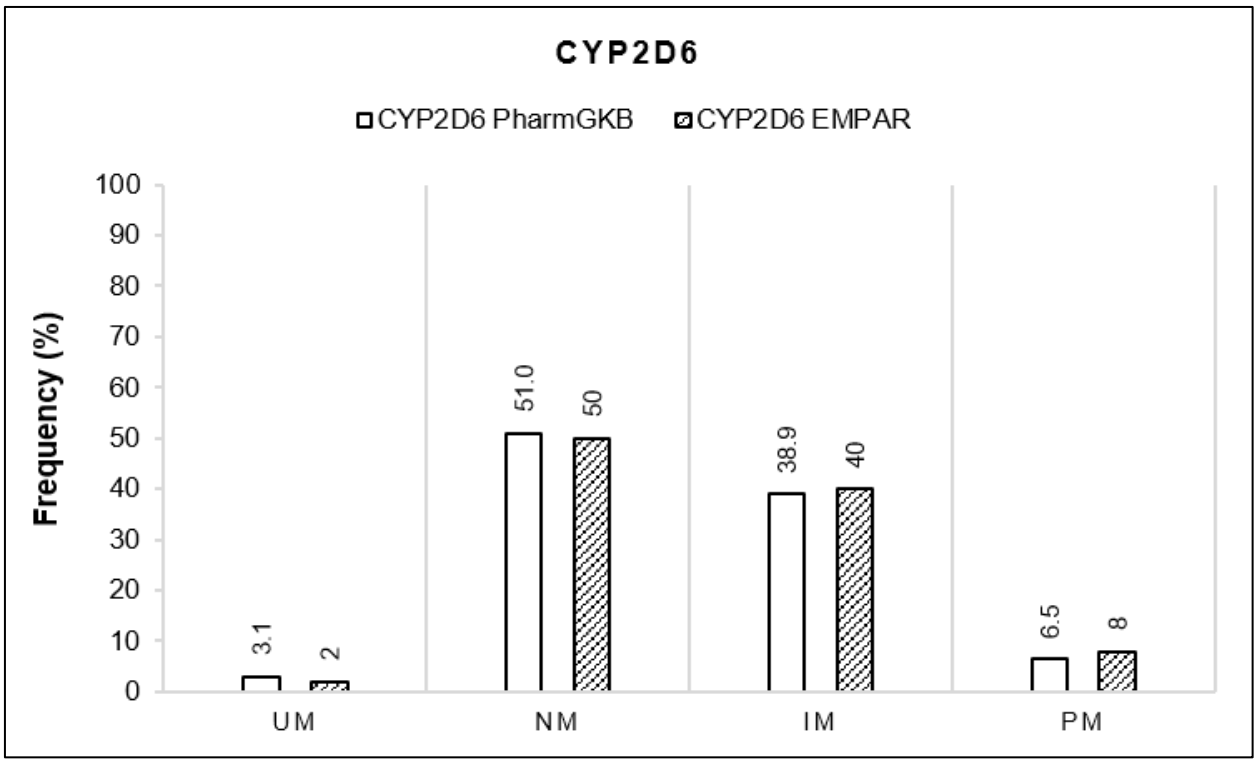


**Figure 7** Frequencies of computed metabolic profiles (*CYP2D6*) compared to reference data. UM: ultra-rapid metabolizer, NM: normal metabolizer, IM: intermediate metabolizer, PM: poor metabolizer. The VeriDose CYP2D6 CNV panel was applied to compute the ultra-rapid metabolizer status (UM) for *CYP2D6*. In addition, this panel reports the (*CYP2D6-CYP2D7*) hybrid allele information for Exon9, *68 and *13 variants. The overall phenotype computation was improved by this information.

Diplotype-Diplotype combinations per collective

Anticoagulant/antiplatelet collective

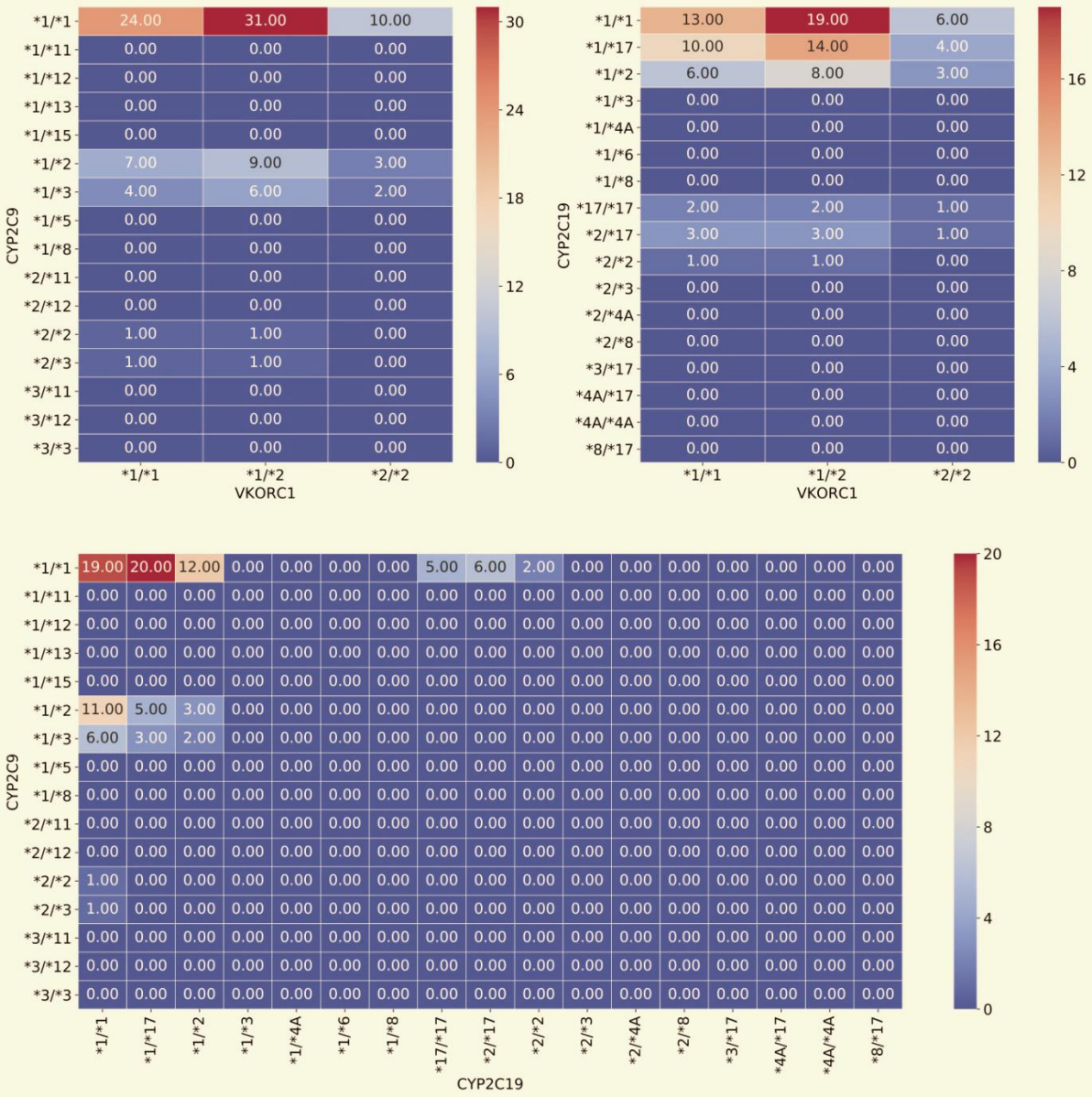


**Figure 8** Frequencies (%) of Diplotype-Diplotype combinations of *CYP2C9*, *CYP2C19* and *VKORC1*. Highest frequencies are represented by *CYP2C9**1/*1 with *CYP2C19**1/*17 and *CYP2C9**1/*1 with *CYP2C19**1/*. For *VKORC1*, the most frequent combination was *1/*1 and *1/*2 (*CYP2C(1)9* and *VKORC1*). The highest haplotype deviations from the normal function were *2 for *CYP2C9*/*VKORC1* (decreased function) and *17 (increased function) for *CYP2C19* with potential effect on drug therapy.

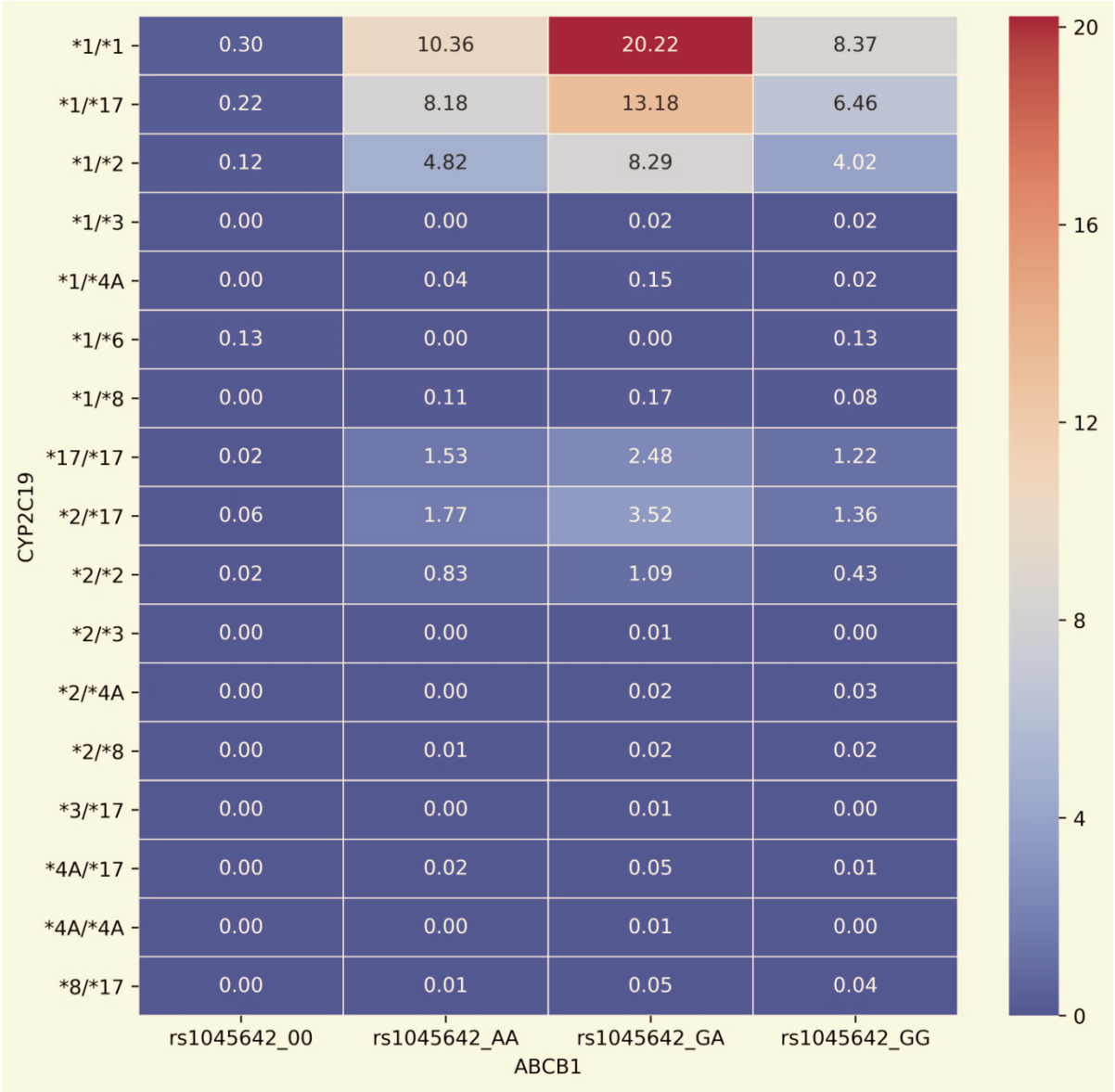


**Figure 9** Frequencies (%) of Diplotype-Diplotype combinations between *ABCB1* and *CYP2C19*

Cholesterol lowering drug collective

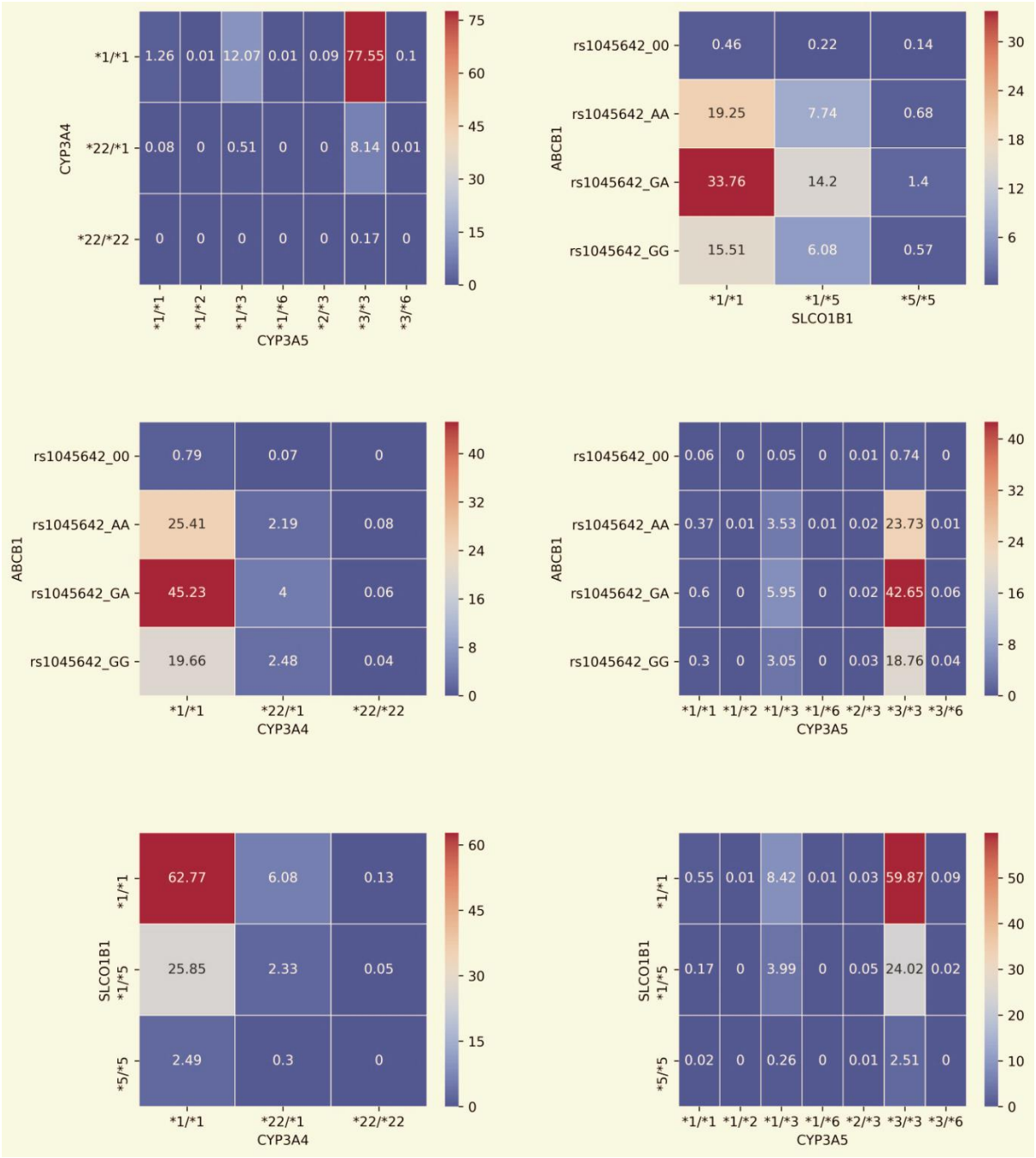


**Figure 10** Frequencies (%) of Diplotype-Diplotype combinations between *ABCB1*, *CYP3A4*, *CYP3A5* and *SLCO1B1*. Highest frequencies could be observed in combination with the *CYP3A5* *3/*3 (poor function) diplotype. In the EMPAR study *CYP3A5* *3/*3 with *CYP3A4* *1/*1 (normal function) were the most frequent observed combination. Similar results were obtained for *SLCO1B1* *1/*1 to any other gene combination analyzed, whereas a combination with the *ABCB1* transporter rs1045642_GA (MW) diplotype appeared as most prevalent result.

## Note:

Data from de Keyser et al. (2013)[1], Ufer et al. (2009)[2] and Belmonte et al. (2017)[3] were analogous to EMPAR data translated into phenotypes.


1. de Keyser CE, Peters BJM, Becker ML, et al. The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics. 2014;24(1):43-51. doi:10.1097/FPC.0000000000000018

2. Ufer M, Mosyagin I, Muhle H, et al. Non-response to antiepileptic pharmacotherapy is associated with the ABCC2-24C>T polymorphism in young and adult patients with epilepsy. Pharmacogenet Genomics. 2009;19(5):353-362. doi:10.1097/FPC.0b013e328329940b

3. Belmonte C, Ochoa D, Román M, et al. Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 Polymorphisms on Pharmacokinetics and Safety of Aripiprazole in Healthy Volunteers. Basic Clin Pharmacol Toxicol. 2018;122(6):596-605. doi:10.1111/bcpt.12960