E-P18.01

Comparison of genetic variation in ADME genes between the Croatian population and Europeans (gnomAD database)

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INTRODUCTION

- The pharmacogenetic data have been studied extensively due to their clinical importance in the appropriate drug prescription.
- **Aim:** to determine allele frequencies of 27 most important ADME polymorphisms (20 of them were 1A, 1B or 2A clinical annotation level of evidence) in the **Croatian population** and to compare them with the **European population** data.

MATERIALS & METHODS

- The **27 loci** from 20 ADME genes were genotyped in the Croatian study sample consisted of **430 participants**.
- Allele frequencies were **combined with published data** on the Croatian population (weighted frequencies according to sample sizes).
- The Croatian allele frequencies were compared with the European population average data taken from the **gnomAD database** (selection criteria: control groups only)

RESULTS

Table 1. Variant allele frequencies that showed significant difference ($p<0.05$) between the Croatians and Europeans (gnomAD database) and possible clinical implication.

GENE: SNP	Variant allele frequency (European - gnomAD)	Variant allele frequency (Croatian)	Clinical implication on dose and adverse reactions (ADRs)	Dose needed
ABCB1: rs1045642	0.4608	0.4880 ↑	Digoxin, Fentanyl	↑
CYP2B6: rs2279343	0.0932	0.2430 ↑	Bupropion, Efavirenz	↑
CYP2D6: rs28371725	0.0887	0.1050 ↑	Impact on ADRs of Codeine, Tamoxifen, Amitriptyline, Metoprolol, Venlafaxine, Desipramine	
GSTP1: rs1695	0.3325	0.2980 ↓	Impact on ADRs of Platinum compounds, Cyclophosphamide and Epirubicin	
CYP2A6: rs1801272	0.0261	0.0120 ↓	Nicotin	↑
*CYP2C9*2*: rs1799853	0.1228	0.1470 ↑	Warfarin, Accenocoumarol, Phenytoin	↓
*CYP2C9*3*: rs1057910	0.3325	0.2980 ↑	Antiinflammatory agents, non-steroids, Celecoxib or Diclofenac, Warfarin	↓
VKORC1: rs9923231	0.3488	0.4030 ↑	Warfarin	↓

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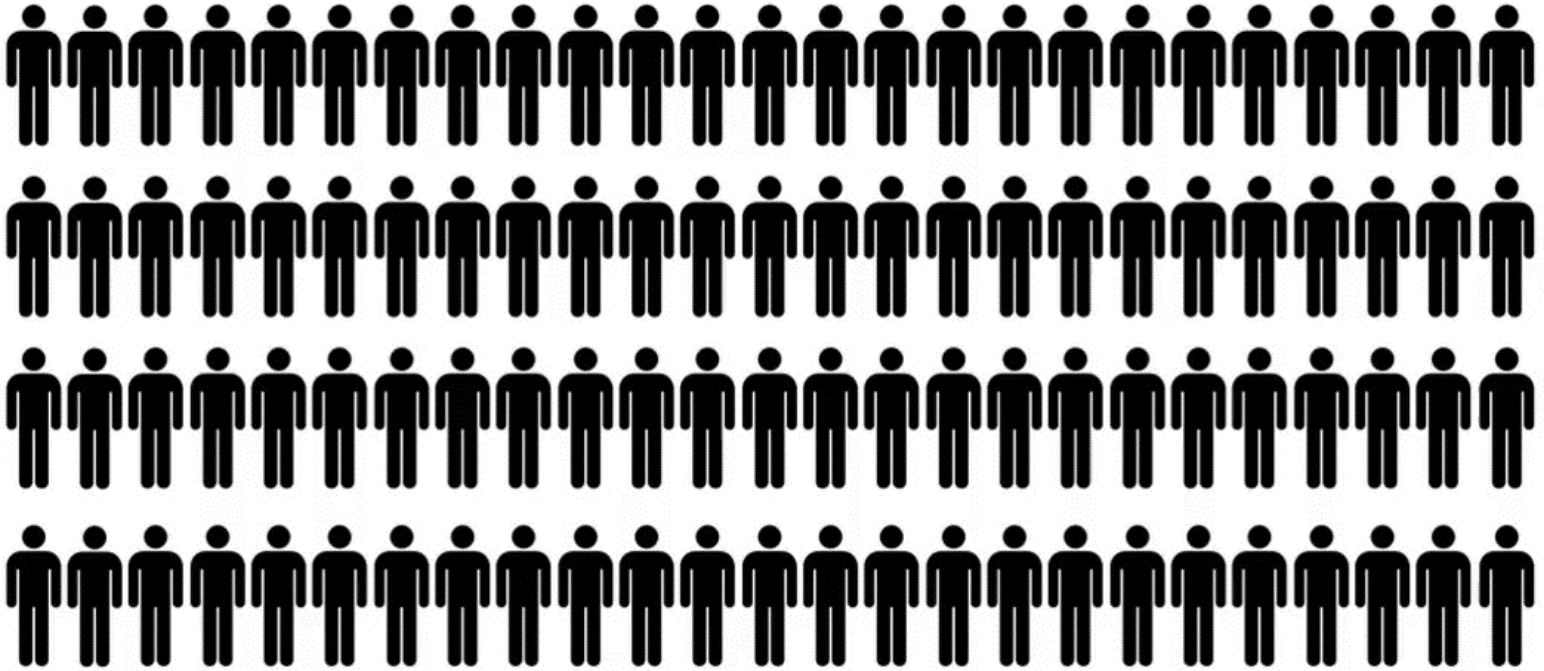

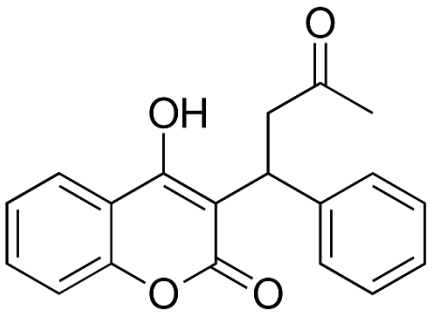

warfarin

76% of the Croatian population carry at least one variant allele

responsible for lower **warfarin** requirement

(*CYP2C9*2*, *CYP2C9*3*, *VKORC1*)

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CONCLUSION

- Compared to the gnomAD European average, the Croatian population showed higher variant allele frequencies in six, and lower variant allele frequencies in two out of the 27 investigated pharmacogenetically relevant ADME loci. Those results imply that in the Croatian population:
  - Lower doses are more frequently required for: warfarin, phenytoin and celecoxib
  - Higher doses are more frequently required for: digoxin, fentanyl, bupoprion and efavirenz
- Clinically most relevant findings in the Croatian population are higher variant allele frequencies in all the three investigated loci (*VKORC1, CYP2C9*2* and *CYP2C9*3*) related to lower warfarin requirements, indicating that 76% of the Croatians carry at least one variant allele at those loci. This finding indicates higher bleeding and over-anticoagulation risk in Croatians, demanding lower drugs` prescription doses.