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Middle Eastern and Asian individuals possess distinct pharmacogenetics profiles compared to Europeans

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INTRODUCTION

Pharmacogenetic analysis can be readily incorporated into routine whole-genome sequence (WGS)-based clinical genetics testing, providing personalized insights into an individual's drug metabolism. Integrating pharmacogenetic information enables more precise medication selection and dosing, helping to minimize adverse reactions and optimize treatment efficacy. Most pharmacogenetic research has focused on individuals of European ancestry, resulting in limited knowledge regarding drug metabolism and efficacy in populations with diverse genetic backgrounds. This study highlights key differences in pharmacogenetic-relevant alleles between European and non-European populations.

METHOD

Subjects: The analysed cohort comprises 746 unrelated individuals (304 females, 442 males) who have been enrolled in WGS clinical genetic testing. 64% of individuals are from the Middle East (Saudi Arabia, Jordan, UAE, Iraq, Kuwait, and Lebanon), 16% from South Asia (Pakistan), and 20% from Europe (Germany, Romania, and Albania).

Methods: PharmCAT version 2.8.3 was used to infer tier 1 and tier 2 pharmacogenetic-relevant haplotypes[1], which include 17 genes and 66 drugs. The distribution of the alleles was investigated in the different populations. For each gene, only cases with a PhamCAT genotype call were included. CPIC standardized nomenclature was used. Functional annotations for the alleles were retrieved from pharmgkb.org. P-values were calculated using Fisher's exact test.

RESULTS

The pharmacogenetic constellation of understudied populations (Middle East and South Asia) differs significantly from European populations. The following are three examples of these differences.

G6PD

Glucose-6-Phosphate Dehydrogenase (G6PD) is involved in the metabolism of several drugs, such as Lidocaine, Glipizide, Chloroquine, Ascorbic Acid, Dapsone, and Quinine. We found 9% of females in the Middle East and South Asia groups are carriers of deficient G6PD haplotypes, including two homozygous cases. All individuals in the European group carried the reference haplotype. Our results reveal a significant difference in G6PD allele distribution between Middle Eastern/South Asian and European populations (p-value<0.01).

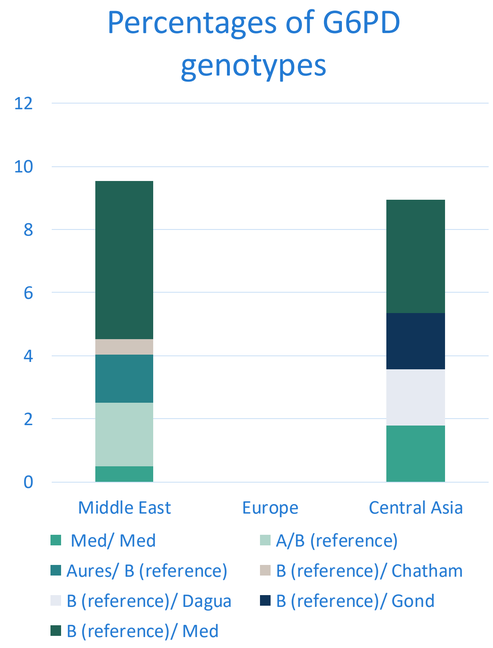

Figure 1: The distribution of deficient G6PD haplotypes across populations. The label "**Med**" stands for Mediterranean, Dallas, Panama, Sassari, Cagliari, Birmingham.

CYP2C9

Cytochrome P-450 2C9 is a liver enzyme involved in the metabolism of many drugs, including anticoagulants, oral hypoglycemics, and NSAIDs. About 5% of the Middle Eastern and South Asian cohort carry a deficient CYP2C9 haplotype, expected to result in poor metabolism of Ibuprofen. None of the European cohort carries the deficient CYP2C9 haplotypes (p-value <0.05).

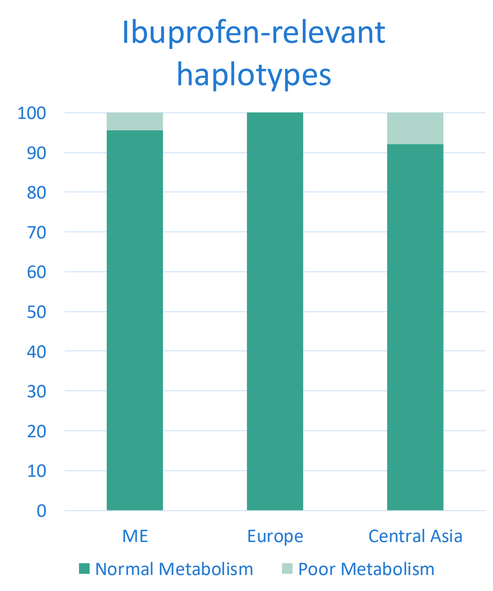

Figure 2: Proportion of deficient and wild-type CYP2C9 haplotypes associated with Ibuprofen metabolism by population.

CYP2C19

Cytochrome P-450 2C19 is an essential enzyme for the metabolism of over 10% of drugs in clinical use, such as diazepam, clopidogrel, omeprazole, pantoprazole, and atazanavir.

The percentage of non-functional CYP2C19 alleles is higher in the South Asian population. However, the difference is not statistically significant. Importantly, non-functional haplotypes range from 20% to 50% across the different populations, warranting dosage adjustment for many commonly prescribed drugs.

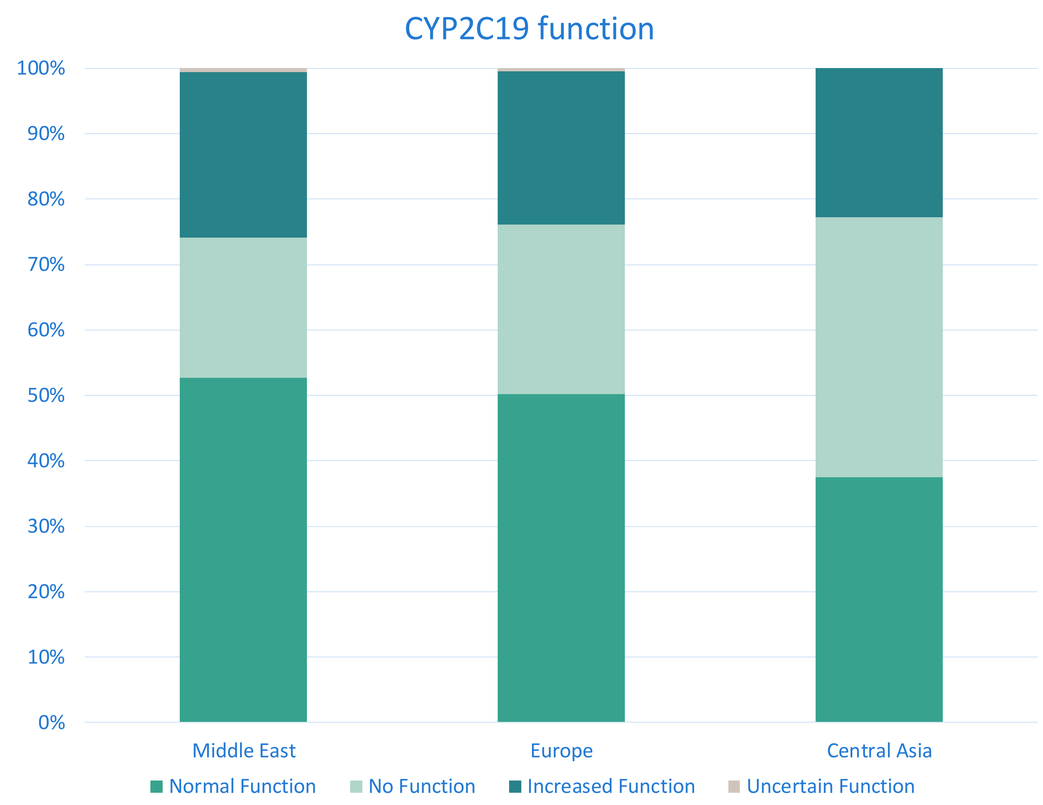

Figure 3: Proportion of CYP2C19 haplotypes associated with functionality by population.

CONCLUSION

Individuals from the Middle East and South Asia have unique pharmacogenetic profiles for genes such as G6PD, CYP2C9, and CYP2C19, differing significantly from those of European populations. Understanding these genetic differences is essential for selecting the right medications and dosages, helping to prevent serious side effects and improve treatment outcomes, ultimately leading to safer and more effective patient care.

CONFLICT OF INTEREST STATEMENT: RA, EP and NA are current employees at Arcensus GmbH.

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References:

[1] **Sangkuhl Ket al.** Pharmacogenomics Clinical Annotation Tool (PharmCAT). Clin Pharmacol Ther. 2020 Jan;107(1):203-210. doi: 10.1002/cpt.1568. Epub 2019 Sep 17. PMID: 31306493; PMCID: PMC6977333.

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