Pharmacogenetic screening relevant polymorphisms on antiretroviral therapy in a HIV Portuguese population.

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Review

Several factors cause heterogeneity of response to antiretroviral therapy. Genetic polymorphisms, particularly in metabolizing enzyme, cytochrome P450 isoenzymes and transport proteins MDR, MRP and SLC, may cause pharmacokinetic variability in some ARVs, leading to viral failure, drug toxicity and may explain the interpatient variability for drug absorption pathways.

Objectives

Characterize the genetic profile of HIV-infected patients in the Portuguese Population, from Santa Maria Hospital, Lisbon, Portugal.

Single-Nucleotide Polymorphism

A total of 15 SNP, with pharmacogenetics relevance, located at 9 different genes, were genotyped by Microarray analysis. The SNP were selected based on their involvement in drug metabolism and according to the collection provided by the TaqMan® Drug Metabolism Genotyping Assays.

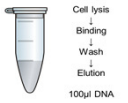
SNP ID	Gene	Assay ID	Alleles tested	n Samples tested
rs7662029	UGT2B7	C__30720663_20	G/A	345
rs1045642	ABCB1	C___7586657_20	G/A	359
rs9282564	ABCB1	C___2614970_10	C/T	349
rs1128503	ABCB1	C___7586662_10	G/A	353
rs2032582	ABCB1	C_11711720D_40	C/T	354
		C_11711720C_30	C/A	354
rs2125739	ABCC10	C__16173668_10	C/T	340
rs1751034	ABCC4	C___1901918_30	C/T	357
rs2274407	ABCC4	C__16181780_20	C/A	345
rs28399435	CYP2A6	C__30634234_10	C/T	348
rs8192726	CYP2A6	C__29560333_20	C/A	357
rs3745274	CYP2B6	C___7817765_60	G/T	356
rs28399499	CYP2B6	C__60732328_20	C/T	354
rs776746	CYP3A5	C__26201809_30	C/T	332
rs41303343	CYP3A5	C__32287188_10	A/DEL	348
rs2307424	NR1I3	C__25746794_20	G/A	349
rs4149056	SLCO1B1	C__30633906_10	C/T	345

Experimental Methods

Sample

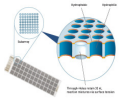
1ml blood of 27 patients infected with HIV1 or co-infected with HBV/C

Extraction DNA



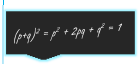
PerfectPure DNA Blood Kit (5Prime)

Microarray



- TaqMan® Genotyping Assays
- OpenArray® Technology

Statistic Analysis



Hardy-Weinberg R package based on X^2 – test

Population Characteristics

Is composed of 367 individuals infected with HIV-1 receiving ARV therapy. In terms of gender, 253 are male and 114 are female. In relation to the race are 275 Caucasian, 114 African and 38 unknown.

Results

All SNP were in Hardy-Weinberg equilibrium except for CAR NR1I3 rs2307424 (p=0.048), CYP2A6 rs28399435 (p= 0.000) and CYP3A5 rs776746 (p=<0.0001), table 1.

Genotype frequencies for the gene/SNP are not the same among the groups Caucasian and African (p-value < .05). As an example we show 2 SNPs with significance CAR NR1I3 rs2307424 (p=0.005), and CYP3A5 rs776746 (p=0), table 2.

The comparison of SNP frequencies by gender doesn't show statistical significance,, except for CYP3A5 rs776746 (allele frequencies p=0.049) (genotype frequencies p=0.007), table 3.

Gene/SNP	N	Genotype	n	Freq.(%)	95% CI	P-value
CAR NR1I3	348	CC	152	43.68	(38.4,49.1)	0.048*
rs2307424		CT	143	41.09	(35.9,46.5)	
		TT	53	15.23	(11.7,19.5)	
		C	447	64.22	(60.5,67.8)	
		T	249	35.78	(32.2,39.5)	
CYP2A6	345	AA	41	11.88	(8.8,15.9)	0.000*
rs28399435		AG	30	8.70	(6.0,12.3)	
		GG	274	79.42	(74.7,83.5)	
		A	112	16.23	(13.6,19.2)	
		G	578	83.77	(80.8,86.4)	
CYP3A5	354	AA	28	7.91	(5.4,11.4)	<0.0001*
rs776746		AG	67	18.93	(15.1,23.5)	
		GG	259	73.16	(68.2,77.7)	
		A	123	17.37	(14.7,20.4)	
		G	585	82.63	(79.6,85.3)	

Table:1 Genotype and allele frequencies of the analysed polymorphisms

Gene/SNP	Genotype /Allelic	Caucasian	(%)	African	(%)	P-value
CAR NR1I3	CC	90	31.58	29	10.18	0.005*
rs2307424	CT	104	36.49	13	4.56	
	TT	45	15.79	4	1.4	
	C	284	49.82	71	12.46	0.002*
	T	194	34.04	21	3.68	
CYP3A5	AA	0	0	23	7.9	0 (a)*
rs776746	AG	41	14.09	16	5.5	
	GG	204	70.1	7	2.41	
	A	41	7.04	62	10.65	0*
	G	449	77.15	30	5.15	

Table:2 Allele and genotype frequencies and percentage of SNPs of CAR NR1I3 and CYP3A5 Genes per race.

Gene/SNP	Genotype /Allelic	Male	(%)	Female	(%)	P-value
CYP3A5	AA	10	3.08	14	4.31	0.007*
rs776746	AG	47	14.46	15	4.62	
	GG	168	51.69	71	21.85	
	A		67		43	0.049*
	G		383		157	

Table 3: Frequencies and percentage per gender for CYP3A5 rs776746.

Conclusion

With the profile obtained by genetic characterization, performed in this study, we can conclude that the gene CYP3A5 rs776746 evidenced more heterogeneity in the population, according to the literature.

CYP3A5*3 (rs776746) the most common non-functional allele of the gene. Seems to be an import contributor to individual and inter rational variation in CYP3A5 mediated metabolism of drugs.

Our study revealed a significant frequency of risk alleles associated with drug efficacy, safety and recommend dosage, namely CYP2A6, CAR N and CYP3A5 rs776746. And therefore could provide clinical useful information on ART in HIV Portuguese population.

Acknowledgements

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