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Frequency of 14 Genetic Variants Associated with Breast Cancer Risk and Treatment in a Colombian Population

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Abstract

Introduction: Genetic variations have been related to risk and treatment efficacy. Many polymorphisms in breast cancer are known to influence susceptibility, breast cancer risk and treatment outcome. Polymorphisms vary among populations; therefore, local studies are necessary.

Objective: To establish the frequency of polymorphisms associated to breast cancer risk and treatment pharmacogenomics in a group of Colombian individuals.

Methods: Data from microarray profiles that include associated polymorphisms with breast cancer treatment were retrospectively collected (Pathway Genomics®). The frequency of theCYP2D6 rs3892097, panel of breast cancer (CAS8 rs1045485, CHEK21100delC, ESR1 rs2046210,FGFR2rs1219648, intergenic_2q35rs13387042, intergenic_8q24 rs13281615, MSRP30 rs10941679, TNRC9 rs3803662,AKAP9 rs6964587, LSP1 rs3817198, MAP3K1rs889312, PALBS1592 delT, ESR1rs3020314) marker polymorphism was analyzed.

Results: Microarray data from 68 men and 92 women were analyzed. All polymorphisms were in Hardy Weinberg equilibrium. Comparisons of genotypesCYP2D6 rs3892097 C/T , CAS8 rs1045485 G/C, panel of breast cancer (CAS8 rs1045485, CHEK21100delC,FGFR2rs1219648, intergenic_2q35rs13387042, intergenic_8q24 rs13281615, MSRP30 rs10941679, TNRC9 rs3803662, LSP1 rs3817198, MAP3K1rs889312, PALBS1592 delT, ESR1rs3020314) were not significantly different to previously published data, the rare alleles found were ESR1 rs2046210 with allele frequencies of C=0.04 and T=0.02. AKAP9 rs6964587 showed a frequency of A=0.005.

Conclusion: The population studied was not significantly different in allele distribution with previously reported data from HAPMAP. Genotypes in Colombian population are similar to other previously studied groups of healthy subjects. The use of genotyping pharmacogenetic polymorphisms will prevent toxicity and adverse effects in tamoxifen treatment (for example in CYP2D6 rs3892097), therefore therapeutic alternatives should be evaluated based on individual pharmacogenetic studies.

Keywords: Colombian; Pharmacogenomics; Breast cancer

Introduction

Advances in technology have made multigene testing, or "panel testing," a practical option when looking for genetic variants that may be associated with a risk of breast cancer and outcome to treatment. Use of pharmacogenomics will optimize treatment and lower health costs. In this context, it is necessary to study disease associations and pharmacogenetic polymorphisms in populations to optimize disease treatment. In the case of breast cancer, tamoxifen metabolism related polymorphisms are associated to treatment, but the frequency is not known in Colombian population.

Currently using different platforms to process and analyze samples can simultaneously identify genetic variants associated with susceptibility, clinical outcomes and drug response. For example the spectrum of the frequency of the MTHFR gene polymorphism C677T in a group of healthy Colombian individuals was previously determined to evaluate the genetic background in relation to disease susceptibility and pharmacogenetic applications, the results for the C/C and C/T genotypes in a Colombian population were similar to other previously studied groups of healthy subjects. Subjects from our population might be at risk of developing diseases associated with MTHFR polymorphisms and might present toxicity and adverse effects if treated with MTX, which suggests the need to evaluate therapeutic alternatives based on individual pharmacogenetic studies [1].

In the case of breast cancer the response to several hormone therapeutics, such as tamoxifen are mediated by the action of CYP2D6, which is highly polymorphic and genotypes has been identified allowing to classify patients as ultra-rapid, normal and poor metabolizers.

Genetic variants in certain genes have been associated with early cancer risk [2], risk of developing cancer [3] and susceptibility to cancer [4]. CYP2D6* 4 variant (rs3892097) is associated with response to tamoxifen, since patients with Tallele will present slow metabolism and therefore need dose adjust mentor use of alternative therapy [5]. In the case of CAS8rs1045485 Callele is associated with a lower risk of breast cancer [6,7]. ESR1rs2046210 has been associated with risk of developing breast and endometrial cancer in Chinese women [8-10], and variant Chas been associated with ER-negative but not ER-positive breast cancer (P>0.05). These findings provide further evidence for distinct etiological pathways associated with invasive ER-positive and ER-negative breast cancer in younger women and women of African ancestry [11]. FGFR2rs1219648 similarly, showed association with risk of developing breast cancer in Chinese [12] and Indian population [13]. Polymorphism rs13387042-2q35 (G/A), has been associated with breast cancer risk only among postmenopausal women who never used hormone therapy [14],on the other hand the GG genotype of SNP rs13281615 plays a role in breast cancer through PVT1 expression, during oncogenesis, «protective» mutations could occur [15]. Also MSRP30 rs10941679 was significantly associated with BCIS (Breast cancer in situ) risk [16]. ForTNRC9 rs3803662, allele GG increased the risk of breast cancer in codominant inheritance (OR=2.19, 95% CI: 1.19-4.02) and recessive genetic models (OR=2.06, 95% CI: 1.15-3.70) [17]. Moreover, the variant rs6964587 was associated with increased breast edema due to radiotherapy after the following 5 years (Beta, 0.22; 95% confidence interval, 0.09-0.34; P = 7×10-4) [18] and increased to risk of breast cancer [19]. LSP1 rs3817198 has been associated with mammographic density in genome-wide studies [20]. Likewise MAP3K1rs889312 has been associated with breast cancer risk in women of European ancestry [21] and ESR1rs3020314showed stronger associations in ER-positive [22]. Finally in AKAP9 the minor T allele of 7q21-rs6964587 was associated with breast cancer risk under a recessive model (OR 1.07, 95% CI 1.00 to 1.13, p = 0.04) [23].

Knowledge of Colombian disease associated polymorphism frequencies will allow to establish National Health policies to improve health and treatment outcome.

Methods

Population

A retrospective cross-sectional study in 160 healthy Colombian individuals over 18 years was conducted using molecular genetics profiling, age ranges between 18 and 74 years with a mean of 40.07 years. DNA samples were collected from saliva samples in "Instituto de Referencia Andino" including all applications from medical orders and/or direct individuals received between the years 2012 and 2014. All individuals signed an informed consent.

The Healthy Woman DNA Insight™ panel from Pathway Genomics evaluates panel of breast cancer (CAS8 rs1045485, CHEK21100delC, ESR1 rs2046210, FGFR2rs1219648, intergenic_2q35rs13387042, intergenic_8q24 rs13281615, MSRP30 rs10941679, TNRC9 rs3803662, AKAP9 rs6964587, LSP1 rs3817198, MAP3K1rs889312, PALBS1592 delT, ESR1rs3020314).

The pharmacogenetic polymorphism panel from Pathway Genomics® in Medication DNA Insight TM genetic test evaluates 15 metabolism associations for drug metabolism, including Tamoxifen (CYP2D6*4), in addition to: Abacavir® hypersensitivity, aminoglycoside-induced ototoxicity, response to beta blockers, carbamazepine hypersensitivity, clopidogrel metabolism, estrogen supplementation, alpha interferon, metoprolol metabolism, metabolism and hypersensitivity to phenytoin, proton-pump inhibitor, simvastatin induced myopathy, metabolism of voriconazole and warfarin.

DNA microarrays were used to measure expression levels of probes, corresponding to alleles in the CAS8 rs1045485, CHEK21100delC, ESR1 rs2046210,FGFR2rs1219648, intergenic_2q35rs13387042, intergenic_8q24 rs13281615, MSRP30 rs10941679, TNRC9 rs3803662,AKAP9 rs6964587, LSP1 rs3817198, MAP3K1rs889312, PALBS1592 delT, ESR1rs3020314 genes. Each microarray position contains 10-12 picomoles of a specific DNA sequence under high stringency. Probe-target hybridization was detected and quantified by fluorophores attached to the probe. The frequency of the polymorphism substitution in the genes markers was analyzed.

Each participant was identified by a code used in a database, where the descriptive analysis for continuous variables such as age was performed with measures of central tendency and

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Shapiro Wilk normality test. The description of categorical variables (origin, sex, genotype and allele) was performed by frequency analysis. Given the variable nature of the study association levels, they were evaluated by a Chi square test (X^2) with a confidence level of 95%. In addition, Hardy Weinberg equilibrium was tested. Data base designed in Access includes the following variables. That were Collected: Code anonymity of each individual, age, gender, date of birth, maternal ancestry, paternal ancestry, nationality, CYP2D6 rs3892097, panel for breast cancer (CAS8 rs1045485, CHEK21100delC, ESR1 rs2046210, FGFR2rs1219648, intergenic_2q35rs13387042, intergenic_8q24 rs13281615, MSRP30 rs10941679, TNRC9 rs3803662,AKAP9 rs6964587, LSP1 rs3817198, MAP3K1rs889312, PALBS1592 delT, ESR1rs3020314).

Table 1: Allele frequency comparison between a Colombian population in the present study and HapMap database.

Gen -SNP	Ref SNP Alleles	MAF	Ancestral Allele	Populatio-ngenetics ALL	1000 Genomes Browser Allelesfrecuencies CLM	Observed IRA N:160	Allelesfrecuencies IRA	HW
CYP2D6*4 rs3892097	C/T	T:0.09	C	C= 0.91	C=0.8351	C/C:64	C=0.903	X2 = 2,71
				T= 0.09	T=0.1649	T/T:2	T=0.087	X2 test P value = 0,099
						C/T-T/C:11		
						NI:78		
						S.I:5		
CAS8 rs1045485	C/G	C: 0.05	G	G= 0.95	G=0.9149	G/G:75	G=0.94	X2 =0,401
				C= 0.05	C=0.0851	G/C-C/G:11	C=0.06	X2 test P value =0,526
					-	NA:69		
					-	S.I: 5		
CHEK21100delC	Theprotein-truncating					C/C:86		
						S.I:5		
						NA:69		
ESR1 rs2046210	G/A	A: 0.41	A	G= 0.41	G=0.7340	G/G:53	G=0.74	X2 =3,082
				A= 0.59	A=0.2660	A/A:7	A=0.20	X2 test P value = 0,079
						C/C:2	C=0.04	
						A/G-G/A:21	T=0.02	
						C/T-T/C:3		
						NA:69		
						S.I:5		
FGFR2	A/G	G: 0.41	A	A= 0.59	A=0.6436	G/G:12	A= 0.64	X2 =0,149
rs1219648				G= 0.41	G=0.3564	A/A:36	G=0.36	X2 test Pvalue = 0,699
						A/G-G/A:38		
						NA:69		
						S.I:5		
intergenic_2q35	A/G	A: 0.47	G	A= 0.47	A=0.4149	G/G:30	A=0.42	X2 =0,169
rs13387042				G= 0.53	G=0.5851	A/A:16	G=0.58	X2 test P value = 0,68
						G/A-A/G:40		
						NA:69		
						SI:5		
intergenic_8q24	A/G	G: 0.49	A	A= 0.51	A=0.4681	G/G:23	A=0.46	X2 =0,865
rs13281615				G= 0.49	G=0.5319	A/A:16	G=0.54	X2 test P value = 0,352
						G/A-A/G:47		
						NA:69		
						SI:5		

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MSRP30 rs10941679	A/G (FWD)	G: 0.32	A	A= 0.68	A=0.7021	G/G:10	A=0.65	X2 =0,048
				G= 0.32	G=0.2979	A/A:36	G=0.35	X2 test P value = 0,825
						G/A-A/G:40		
						NA:69		
						SI: 5		
TNRC9 rs3803662	A/G	A: 0.44	G	A= 0.44	A=0.4149	G/G:34	A=0.39	X2 =0,782
				G= 0.56	G=0.5851	A/A:15	G=0.61	X2 test P value = 0,376
						G/A-A/G:37		
						NA:69		
						SI:5		
AKAP9 rs6964587	G/T (FWD)	T:0.37	T	G= 0.63	G=0.5585	G/G:29	G=0.580	X2 = 0,0059
				T= 0.37	T=0.4415	T/T:15	T=0.415	X2 test P value = 0,938
						G/A-A/G:1	A=0.005	
						G/T-T/G:41		
						N/A:69		
						SI:5		
LSP1 rs3817198	C/T (FWD)	C:0.22	T	T= 0.78	T=0.7713	C/C:3	T=0.75	X2 = 1,865
				C= 0.22	C=0.2287	T/T:46	C=0.25	X2 test P value = 0,172
						C/T-T/C:37		
						N/A:69		
						SI:5		
MAP3K1	A/C (FWD)	C:0.39	A	A= 0.61	A=0.5638	A/A:29	A=0.59	X2 =0,085
rs889312				C= 0.39	C=0.4362	C/C:14	C=0.41	X2 test P value = 0,771
						A/C-C/A:43		
						N/A:69		
						SI:5		
PALBS1592 delT	frame-shifting germ-line mutation					T/T:86		
						N/A:69		
						SI:5		
ESR1	C/T (FWD)	T:0.38	C	C= 0.62	C=0.5426	C/C:33	C=0.45	X2 = 0,552
rs3020314				T= 0.38	T=0.4574	T/T:50	T=0.55	X2 test P value = 0,458
						C/T-T/C:72		
						SI:4		
						N/I:1		

Statistical methods

The information is tabulated results available to perform the respective calculation of frequencies of each polymorphism and the Hardy Weinberg was calculate dosing the online calculator Lab HW court additionally the genpop software was used. Later contingency tables were performed double entry with its own Chi squared distribution. The results were transferred to the SPSS statistical program for Windows V20. They were not stratified by ethnic group or socioeconomic levels. Ethical considerations: the study was approved by the Ethics Committee of the National University of Colombia". Additionally available information collected in Hap map Hap Map Genome Browser release #28 (Phases 1, 2 & 3- merged genotypes & frequencies) for general population and Colombian population frequencies for each of the variants tested in this review. Allele Frequency Comparison between Present Study and HAPMAP (Table 1).

Results

No deviation from Hardy Weinberg equilibrium is present, therefore the population included in this study has no significant migration, stratification into subgroups, inbreeding or selection processes. Additionally by contrasting data reported in Hap Map for general population, Colombians of the present study, have no

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significant differences with the sample of Colombian population reported in Hap Map.

Evaluating each particular polymorphism, CYP2D6*4 rs3892097, CAS8rs1045485, MSRP30 rs10941679, rs3817198 LSP1 and MAP3K1 rs889312, the data found in the reports of the present study has greater similarity to those reported for world population, than other Colombian groups.

ESR1 rs2046210 variants C and G have frequencies of 0.04 and 0.02, respectively; similarly, to the appearance AKAP9 rs6964587 allele A was reported: 0.005, the presence of these variants had not been previously reported (Figure 1). The graph shows the allele frequencies of the world population reported in Hap Map in blue, the Colombian population in Hap Map in red and the data from this study in green. In addition to FGFR2rs1219648, intergenic 2q35-rs13387042, intergenic 8q24-rs13281615, rs3803662 and ESR1rs3020314 they retained TNRC9 frequencies reported previously for the Colombian population Hap map.

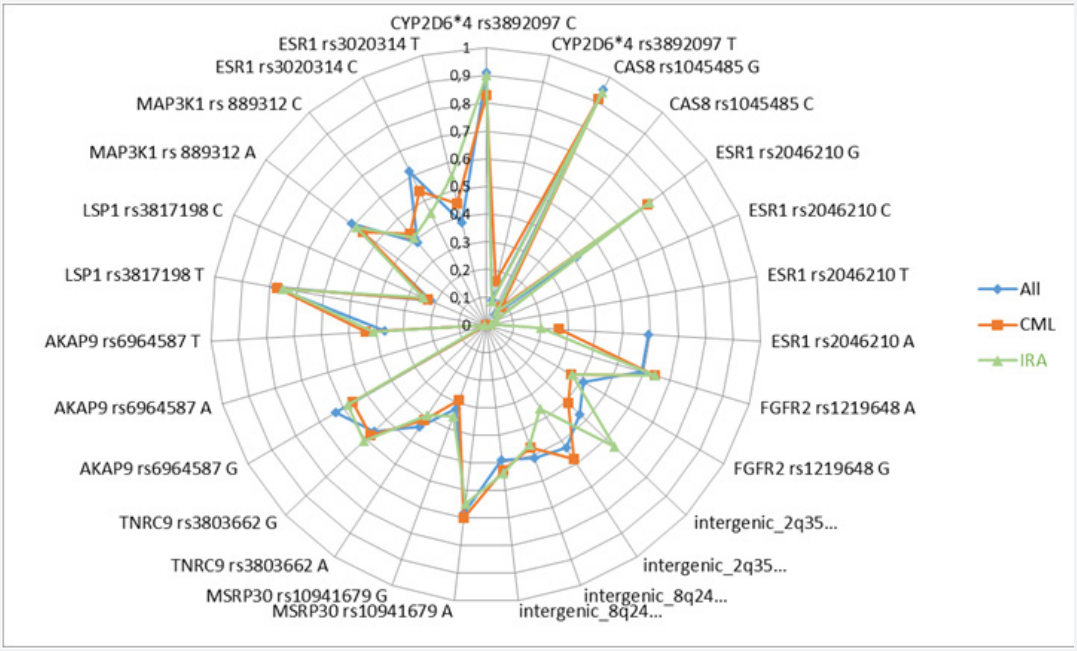

Figure 1: Radial tree, or radial map, for gene frequencies.

Discussion

The need for studies to the Colombian population in order to establish the genetic variants with health implications and thus make prevention programs and personalized therapies that will reduce health costs and ensure a more efficient health care aimed at evidence precision.

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