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Original Research Article

ALLELE AND GENOTYPE DISTRIBUTION OF VOLTAGE-GATED SODIUM CHANNEL GENE POLYMORPHISMS IN SOUTH INDIAN DESCENT

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ABSTRACT

Background: Genetic polymorphisms in voltage-gated sodium channel (VG-SCNA) genes play a significant role in the development of neurological diseases. Various studies have found that there is a significant variation in the genetic makeup of Indians, with other genetic groups having been identified such being Dravidian South Indian population. Hence, we aimed to establish the normative frequency of five SNPs of four VG-SCNA gene subunits in South Indians and wanted to assess the similarity or dissimilarity with other distinct genetic groups. **Materials and Methods:** In this study, we used TaqMan single nucleotide polymorphism (SNP) genotyping assays to evaluate the genotypes of five VG-SCNA genetic polymorphisms associated with neuronal toxicity in 167 healthy unrelated South Indian volunteers on real time thermocycler (ABI Prism 7300, foster city, CA, USA). **Result:** Among 167 healthy volunteers, there were 89 males and 78 females with a mean (SD) age of 25.5 (±5.5) years. The minor allele frequencies of the studied genetic polymorphisms rs2302237 (SCN4A), rs11720524 (SCN5A), rs6746030, rs6754031 (SCN9A), and rs12632942 (SCN10A) were 18.6%, 21.6%, 16.8% 28.8%, and 22.2% respectively. The frequencies of the studied genetic polymorphisms show statistically significant differences from other ethnic groups in five out of the five genetic polymorphisms studied. **Conclusion:** Considerable dissimilarities in frequencies of genetic polymorphisms were found between the South Indian population and other major ethnic populations worldwide with respect to SCN4A (rs2302237), SCN5A (rs11720524), SCN9A (rs6746030, rs6754031), and SCN10A (rs12632942).

INTRODUCTION

It is well known that chemotherapy is used to improve the survival or quality of life of patients with cancer.[1,2] Chemicals in the form of a single agent or in combination with other chemotherapeutic agents, radiotherapy or surgery are used to target cancer cells. Compared to other drugs, chemotherapeutic agents have a narrower therapeutic index and greater potential to cause harmful effects. The cytotoxic nature of these drugs inevitably damages normal tissues which cause longstanding symptoms, deficits and compromises patient benefit.

Oxaliplatin is a platinum based anticancer compound that is used with drugs like gemcitabine, capecitabine, epirubicin and 5-fluorouracil as a combination regimen in the treatment of various malignancies, including colorectal, stomach, ovarian, pancreas and biliary cancers.[3–6] On administration, oxaliplatin gets precipitated in dorsal root ganglion (DRG) and causes peripheral neuropathy which adversely affects the quality of life in around 70% of treated patients as it leads to either decrease in dose or stoppage of the therapy.[7,8]

Voltage-gated sodium channel (VG-SCNA) gene family consist of nine homologous subunits.[9,10] All these VG-SCNA subunits encode the sodium selective ion channels from NaV1.1 to NaV1.9 and play a significant role in electrical signalling process in neurons and other excitable cells.[11,12] These are well distributed in dorsal root ganglion (DRG) neurons and their axons of both the peripheral and central nervous systems.[13] Functional polymorphisms in these VG-SCNA genes can influence their expression or activity. Specifically, VG-SCN4A gene is expressed in skeletal muscle and its polymorphisms have been correlated with periodic paralysis disorders and several myotonias. The

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integral membrane protein encoding VG-SCN5A gene is found primarily in cardiac muscle and mutations in this gene cause autosomal-dominant cardiac disease. Defect in the VG-SCN9A gene play a significant role in nociception signalling and have been linked to channelopathy combined insensitivity to pain and paroxysmal extreme pain disorder, whereas the protein encoded by the VG-SCN10A gene is a tetrodotoxin-resistant SCNA subunit that may be involved in painful peripheral neuropathy.[14–17] Very recently, we described significant association between the VG-SCNA pharmacogenetic variants and the incidence of oxaliplatin induced chronic peripheral neuropathy in South Indian population.[18] India is the second most populous country with various ethnic groups. Hence, genetic variations are familiar among various groups within India and South Indian residents characterize a genetically distinct group.19 Such genetic differences within populations can confound genotype-phenotype association studies and are the major reasons for the conflicting results. Hence, in this study, we tried to establish the normative frequency of five SNPs of four VG-SCNA gene subunits such as SCN4A, SCN5A, SCN9A and SCN10A (details of the polymorphisms are shown in [Table 1]). We also wanted to evaluate the similarity or dissimilarity with various 1000 genome populations such as AFR (African), AMR (American), EUR (European), EAS (East Asian) and SAS (South Asian).

MATERIALS AND METHODS

Study subjects: The study was carried out on healthy volunteers between 18 and 28 years of age. Unrelated healthy volunteers from the general population, residing in the Southern states of India (Tamil Nadu, Telangana, Kerala, Karnataka, and Andhra Pradesh) for three consecutive generations were designated for the study. After explaining the procedures, written informed consent was obtained from each participant. The research protocol was approved by the Institute Ethics Committee. The study was in compliance with the good clinical practice according to the principles of the Declaration of Helsinki.

DNA extraction and genotyping of selected SNPs in the study: Five mL of venous blood sample was collected from each study subject in tubes containing 10% ethylene diamine tetra acetic acid (EDTA) and centrifuged at 2500 RPM for five minutes. The plasma was discarded and the pellets containing lymphocytes along with red blood cells were stored at −80 OC until DNA extraction. The genomic DNA was extracted by the standard phenol–chloroform extraction method 20 and was quantified by using multi-analyzer (TECAN Infinite M200, Switzerland). After confirming the quality and quantity of DNA, genotyping was carried out for rs2302237 (C__15757352_10), rs11720524 (C_ 30666704_10), rs6746030 (C_29330435_10), rs6754031 (C_29108389_10), rs12632942 (C_31683397_10) by Real-Time PCR (ABI Prism 7300, foster city, CA, USA) using validated Real-Time TaqMan single nucleotide polymorphism (SNP) genotyping assays (Applied Biosystems, Foster City, CA, USA) and alleles were distinguished with the sequence detection software version 1.4.

Statistical analyses: The genotype and allele frequencies were determined by direct gene count method. The genotype frequencies were examined for Hardy–Weinberg equilibrium using the chi-square ($\chi 2$) test by comparing the observed frequencies with the expected frequencies. Chi-square test or Fisher's Exact Test was used to calculate the differences in allele frequencies between the study population and populations of different ethnicities. Statistical analysis was done using SPSS (Statistical analysis Package for Social Sciences) version 19.0 and GraphPad InStat (San Diego, USA) version 3.06 software packages. Two sided P values of <0.05 was considered statistically significant.

RESULTS

A total of 167 unrelated healthy subjects were included into the study. Out of these 167, there were 89 males and 78 females. The mean age (±SD) in the study group was 25.5 (±5.5) years. The genotype and allele distribution of all the studied SCNAs SNPs are given in Table 2. Gender based differences between genotyping and allele frequencies not found with the studied SNPs (Table 3). All the SNPs were within Hardy Weinberg Equilibrium probability ($p>0.05$).

SCN4A – rs2302237 (C/T): In our study, C allele and T allele had frequencies of 81.4% and 18.6% respectively. The homogenous CC and TT genotypes were found in 67.6% and 4.8%, while the heterozygous CT genotype was present in 27.5%. The allele frequencies were same as South Asians and other population like Americans and Africans. The minor T (18.6%) allele was lower in the present study when compared to Europeans (36.9%) and East Asian population (30.7%).

SCN5A- rs11720524 (C/G): The genotype frequencies for rs1172052 were CC = 62.9%, CG = 35.1% and GG = 6.0%. The minor allele G had a frequency of 21.6%, the lowest when compared to European (40.6% and African populations (30.1%).

SCN9A-rs6746030 (G>A): The genotype distributions of rs6746030 were 68.8%, 30.0% and 1.2% respectively. The G allele frequency was calculated to be 83.2% and the minor allele A frequency was 16.8%. The allele frequencies were found to be statistically divergent from East Asians. The minor allele (A) frequency in East Asian population was just 4.1% while in our study population it was 16.8%. We didn't find any statistically significant difference with other population of the 1000 genome project data.

SCN9A-6754031 (T/G): The genotype distributions for SCN9A- rs6754031 were 54.5% (TT), 41.3%

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(TG) and 4.2% (GG) respectively. The T allele frequency was calculated to be 75.1% and the minor allele G frequency was 24.9%. The allele frequencies were found to be statistically divergent from Europeans (p=0.03). The minor allele (G) frequency in European population was 40.3% while in our study population it was 24.9 %. We didn't find any statistical significant difference with other population of the 1000 genome project data.

SCN10A-rs12632942 (A/G): The observed genotype and allele distributions for rs12632942 were AA (61.7%), AG (32.3%), GG (6.0%) and A (77.8%), G (22.2%) respectively. The minor allele G frequency was lower in African and American population when compared to the present study population and we found statistically significant difference with East Asian population as they had higher minor allele frequency [Table 4].

Table 1: Characteristic features of the voltage gated sodium channel gene polymorphisms in the study cohort.

Gene	SNP type	SNP ID/ rs ID	Allele change	Gene location	Assay ID (Applied Biosystems)
SCN4A	Intron	2302237	C/T	Chr.17:63971347	C__15757352_10
SCN5A	Intron	11720524	C/G	Chr.2:240878099	C_30666704_10
SCN9A	Missense	6746030	G/A	Chr.2:166242648	C_29330435_10
SCN9A	Intron	6754031	T/G	Chr.2:166298928	C_29108389_10
SCN10A	Missense	12632942	A/G	Chr.3:38723507	C_31683397_10
SNP- Single Nucleotide Polymorphism					

Table 2: Genotype distribution of selected SNPs (observed and expected) in healthy South Indians and status of Hardy-Weinberg Equilibrium

Gene	SNP	Genotypes	Genotype frequency (%)		Chi square value	P - value	HWE
			Observed	Expected			
SCN4A	rs2302237						
		CC	67.6	66.2	0.8	0.8	yes
		CT	27.5	30.3			
		TT	4.8	3.5			
SCN5A	rs11720524						
		CC	68.9	66.4	2.86	0.4	yes
		CG	25.1	30.2			
		GG	6.0	3.4			
SCN9A	rs6746030						
		GG	68.8	70.2	1.1	0.7	yes
		AG	30.0	27.2			
		AA	1.2	2.6			
	rs6754031						
		TT	54.5	56.5	1.18	0.7	yes
		TG	41.3	37.3			
		GG	4.2	6.2			
SCN10A	rs12632942						
		AA	61.7	60.6	0.4	0.7	yes
		AG	32.3	34.5			
		GG	6.0	4.9			
HWE - Hardy Weinberg Equilibrium *p value greater than 0.05 indicates the polymorphisms within Hardy Weinberg Equilibrium							

Table 3: Gender wise allele and genotype frequency distribution of selected SNPs in south Indian healthy subjects (N=167)

GENE (SNP)	Genotype frequency , N			Allele frequency, n (%)		P value
SCN4A-rs2302237	**CC**	**CT**	**TT**	**C**	**T**	
Male (89)	55	30	04	140 (78.7)	38 (21.3)	0.3
Female (78)	58	16	04	132 (84.6)	24 (15.4)	
SCN5A-rs11720524	CC	CG	GG	C	G	
Male (89)	58	28	03	144 (80.9)	34 (19.1)	0.4
Female (78)	47	24	07	118 (75.6)	38 (24.4)	
SCN9A-rs6746030	GG	AG	AA	G	A	
Male (89)	68	21	00	157 (88.2)	21 (11.8)	0.1
Female (78)	47	29	02	123 (78.8)	33 (21.2)	
SC9A-rs6754031	TT	TG	GG	T	G	
Male (89)	46	38	5	130 (73.0)	48 (17.0)	0.6
Female (78)	45	31	2	121 (77.5)	35 (22.5)	
SCN10A-rs12632942	AA	AG	GG	A	G	
Male (89)	60	25	04	145 (81.5)	33 (18.5)	0.3
Female (78)	43	29	06	115 (73.7)	41 (26.3)	
N-total number of patients, n-the number of alleles are calculated relative to the total number of chromosomes. p>0.05 is considered statistically not significant.						

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Table 4: Comparison of genotype and allele frequencies with 1,000 Genome project data

SNP –Genotype/Allele	South Indian N=167	AFR N=661	AMR N=347	EUR N=503	EAS N=504	SAS N=489
SCN 4A- rs2302237 (C>T)						
CC	67.6	79.1	52.4	40.0	48.2	56.9
CT	27.5	20.3	40.1	46.3	42.3	34.6
TT	4.8	0.6	7.5	13.7	9.5	8.6
Alleles						
C	81.4	89.3	72.5	63.1	69.3	74.1
T	18.6	10.7	27.5	36.9**	30.7	25.9
SCN5A- rs11720524(C>G)						
CC	62.9	49.3	46.1	35.6	81.3	70.8
CG	35.1	41.1	45.8	47.7	17.7	26.4
GG	6.0	9.6	8.1	16.7***	1.0	2.8
Alleles						
C	78.4	69.9	69.0	59.4	90.2	83.9
G	21.6	30.1	31.0	40.6	9.8**	16.1
SCN9A- rs6746030 (G>A)						
GG	68.8	80.5	77.6	76.9	92.1	67.1
GA	30.0	18.6	21.0	20.9	7.7	29.2
AA	1.2	0.9	1.4	2.2	0.2	3.7
Alleles						
G	83.2	89.8	88.0	87.4	95.9	81.7
A	16.8	10.2	12.0	12.6	4.1**	18.3
SCN9A - rs6754031 (T>G)						
TT	54.5	42.2	47.6	63.0	47.8	39.9
TG	41.3	44.3	40.3	47.5	42.3	45.6
GG	4.2	13.5	12.2	16.5	9.9	14.5
Alleles						
T	75.1	64.4	67.7	59.7	68.9	62.7
G	24.9	35.6	32.3	40.3*	31.1	37.3
SCN10A- rs12632942 (A>G)						
AA	61.3	77.3	76.6	56.8	38.9	59.1
AG	32.3	21.2	22.5	37.0	47.0	35.0
GG	6.0	1.5	0.9	6.2	14.1	5.9
Alleles						
A	77.8	87.9	87.9	75.3	62.4	76.6
G	22.2	12.1	12.1	24.7	37.6*	23.4

N, total number of participants in each group , AFR, African; AMR, American; EUR, Europeans; EAS, East Asians; SAS, South Asians; * Two sided P value < 0.05, ** p <0.01, *** p<0.0001

DISCUSSION

The ethnicity and genetic makeup of Indian population are remarkably diverse from other populations worldwide.[19] The south Indian population in which the study was performed belonged to the Dravidian subgroup and they constituted almost 25% of the total Indian population.[20,21]

In this current study, we established the allele and genotype frequency distribution of five genetic polymorphisms of four VG-SCNA gene subunits that are associated with various neurological diseases in 167 South Indian subjects and tested them with 1000 genome project data.

Although the polymorphisms reported in our study had been reported recently and less information was available regarding its global distribution, the outcome of our findings showed remarkable heterogeneity with respect to SCN4A, SCN5A, SCN9A and SCN10A allele and genotype frequencies of south Indians compared to 1000 genome population data. This had made the extrapolation of results of genetic studies performed in other ethnic population to Indian population difficult. Thus the need to perform ethnic population based genetic studies and the role of ethnicity had to be substantiated. To the best of our knowledge, this is the first study from India to provide insight into the allele and genotype frequency distribution of various VG-SCNA genetic polymorphisms.

CONCLUSION

The study has established both the allele and genotype frequency distributions for SCN4, SCN5A, SCN9A and SCN10A (rs2302237, rs11720524, rs6746030, rs6754031, rs12632942 rs12632942) genetic variants in healthy individuals of South Indian population. The outcome of the present study contributes for calculating the sample size which will help in designing further pharmacogenetics association studies of SCNA gene polymorphisms with the development of various neurological diseases like myotonia and peripheral neuropathy.

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